The transition between acute and chronic infections in light of energy control: a mathematical model of energy flow in response to infection

Gang Zhao1, Rainer H. Straub2,† and Michael Meyer-Hermann1,3,†

1Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Rebenring 56, 38106 Braunschweig, Germany
2Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, 93042 Regensburg, Germany
3Institute for Biochemistry, Biotechnology and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany

GZ, 0000-0002-2897-6633; MM-H, 0000-0002-4300-2474

Background: Different parts of an organism like the gut, endocrine, nervous and immune systems constantly exchange information. Understanding the pathogenesis of various systemic chronic diseases increasingly relies on understanding how these subsystems orchestrate their activities. Methods: We started from the working hypothesis that energy is a fundamental quantity that governs activity levels of all subsystems and that interactions between subsystems control the distribution of energy according to acute needs. Based on physiological knowledge, we constructed a mathematical model for the energy flow between subsystems and analysed the resulting organismal responses to in silico infections. Results: The model reproduces common behaviour in acute infections and suggests several host parameters that modulate infection duration and therapeutic responsiveness. Moreover, the model allows the formulation of conditions for the induction of chronic infections and predicts that alterations in energy released from fat can lead to the transition from clearance of acute infections to a chronic inflammatory state. Impact: These results suggest a fundamental role for brain and fat in controlling immune response through systemic energy control. In particular, it suggests that lipolysis resistance, which is known to be involved in obesity and ageing, might be a survival programme for coping with chronic infections.

1. Introduction

Brain, gut and immune system are part of a complex network with interactions mediated by molecules, cells and wired connections [1–3]. Knowledge concerning interactions in this complex network is accumulating, having reached a level that challenges holistic understanding. Energy is needed in all vital subsystems to retain functionality and maintain organ integrity. Accordingly, energy homeostasis is tightly regulated both locally (within-organ level) and globally (trans-organ level). Excess energy is stored in fat tissue and can be released upon increased needs, by mechanisms such as β-adrenergic stimulation of lipolysis [4]. Increased needs are signalled in response to various physiological stresses, for example, immune responses to invading pathogens. We have developed a mathematical model of energy flow between five main vital compartments, thus aiming to explore the potential synergisms and/or energy trade-offs between organs, to provide an holistic understanding of the whole network.

Mathematical models can help in understanding the functional interdependence of the network of interacting subsystems of an organism. Such network models have been developed at various scales, such as genetic networks [5],...
molecular networks connecting different subsystems [6], networks of cellular trafficking between organs [7] and multi-organ networks [8] up to population levels [9]. The systems biology community has developed theories and software tools that incorporate energy conservation laws into biochemical networks based on thermodynamic principles [10–13]. At the same time, mathematical models of metabolic energy regulation, with complexities ranging from simple glucose control loops to neural-endocrine control of appetite involving various kinds of nutrients, have been extensively studied in the field of diabetes and obesity [14–17], as well as in sports physiology [18].

To the best of our knowledge, energy was never a network-focus of interacting organismal subsystems. Here, interactions between organs/tissues are formulated in terms of energy flow, where competition, synergisms and trade-offs on the energy-flow level have been translated to the functional level of participant organs/tissues. Our working hypothesis is that dysregulation of energy homeostasis, and the subsequent trade-offs between various organs/tissues, might explain pathogenesis of various systemic diseases, and reveal a potential advantage of this modelling approach over traditional biomolecular/cellular pathway-based modelling.

We have illustrated the concept by drawing on the example of energy flow adaptation induced by immune responses. Given that an immune response, in particular, the acute phase response, is usually associated with anorexia of various degrees, it is expected that sufficient energy stored in fat tissue or supplied environmentally by food is fundamental to success [19], and that the highly energy-dependent inflammation must cease within several weeks to prevent long-term deterioration [20].

However, chronic inflammation is ubiquitous and has emerged as a shared factor in a variety of diseases, notably type 2 diabetes, cardiovascular disease, chronic obstructive pulmonary disease, cancer, asthma, Alzheimer’s disease and autoimmune diseases like rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus [20,21]. Moreover, inflammatory pathways and their associated molecules are continually being identified as reliable markers of ageing, and as risk factors for diseases associated with ageing [22–24]. Chronic inflammation, whether occurring in the absence of overt infection or due to latent pathogens, leads to immune senescence [25,26]. There is also growing mechanistic evidence that chronic inflammation both accelerates and is exacerbated by systemic ageing processes [27–30]. Although growing fast, our current understanding of the precise aetiology of chronic inflammation, as well as its role in immunity and obesity throughout lifespans, remains woefully insufficient [31,32].

The energy-based modelling work presented in this paper allowed us to reproduce common systemic behaviour in acute infections. Moreover, we were able to formulate conditions for the transition between acute and chronic infections revealing a hitherto unappreciated role played by fat tissue.

2. Results

2.1. A model of energy flow

Energy flow in a network of four connected human organis- mal compartments was formulated in the simplest possible manner, albeit strictly based on known physiological principles (figure 1; electronic supplementary material, Methods):

(1) Stress ($U_b$) and immune ($U_i$) responses (units in kJ d$^{-1}$) regulate energy release from fat by lipolysis ($U_f$) units in kJ d$^{-1}$) [33], and energy uptake ($U_e$ units in kJ d$^{-1}$) by modulation of insulin secretion [34] and resistance [35].

(2) Brain and immune system are mutually regulatory: the immune response ($U_i$) triggers the HPA axis ($U_h$) [36] and limits energy uptake by the brain ($U_b$ units in kJ d$^{-1}$)

Figure 1. Schematic of the energy-flow model. The four compartments of the network comprise brain ($B$), immune system ($I$), blood vessel ($V$) and fat tissue ($F$). Energy enters the system from the gut ($J_g$) for use by the brain ($J_b$), immune system ($J_i$) and other tissues ($J_v$). Fat tissue acts as an energy buffer and blood vessels as a central connector of these compartments. The amount of usable energy in the brain and immune system undercuts their daily usage even under healthy conditions, indicating that these two organs largely rely on energy flow from fat ($J_f$) or gut ($J_g$) to blood ($V$), and subsequently from blood to the brain ($J_b$) and to immune system ($J_i$). Energy flow between compartments is regulated by network variables (symbols linked to signs in the legend; colours depict the regulating compartment). One-sided inhibition operates only when the regulating factor is below its homeostatic level. See text for details. Numbers indicate homeostatic levels of energy in kJ or energy flow in kJ d$^{-1}$. 
Homeostatic levels of usable energy in each compartment were estimated by considering various forms of biomolecules (carbohydrates, lipids, ketone bodies, etc.) in blood, and by assuming a linear relationship between the energy level and the mass of the organ/tissue. Homeostatic energy flow was estimated based on published values. Regulation of energy flow was modelled parsimoniously by assuming the simplest form. Refer to the electronic supplementary material, methods, for a detailed explanation of the model.

2.2. Response to infections and therapies

At first, we challenged the energy flow model at its healthy homeostatic state with a one-time pathogen dose, subsequently inducing competition between pathogen growth and pathogen clearance by the immune response \( (L_I) \). The pathogen clearance rate \( (d_p) \) determined the duration of the infection (figure 2a), as well as the time required to re-establish homeostasis (figure 2b). Below a critical pathogen clearance rate \( (C_{crit}) \) (electronic supplementary material, figure S2), the pathogen persisted and the infection became chronic (figure 2a, negative values). Thus, the model captures acute and chronic infections.

In the acute infection regime, a higher pathogen clearance rate \( (d_p) \) was associated with shorter infection duration (figure 2a) and with a faster return to homeostasis (figure 2b). The infection was associated with weight loss and the fat compartment started a slow recovery only after pathogen clearance (figure 2c). In this example, the pathogen was cleared at day 10 while the fat compartment recovered in more than two months (figure 2c). In the chronic infection regime, the system reached a new steady state associated with a persistent pathogen load. This transition was slow (figure 2b, left of the red point), where higher pathogen clearance rates \( (d_p) \) were associated with lower homeostatic pathogen load (electronic supplementary material, figure S1A) and longer time to reach homeostasis (figure 2b).

Because a lower critical clearance rate \( (C_{crit}) \) indicates facilitated pathogen clearance, we next investigated how this depends on pathogen and host properties (electronic supplementary material, figure S2). The pathogen replication rate \( (r_p) \) and the carrying capacity \( (P_{max}) \) were the most sensitive pathogen properties (electronic supplementary material, figure S2E,F). Higher values increased infection duration and \( C_{crit} \). Part of the host factors are parameters \( v_b, v_i \) and \( v_l \) (defined in figure 2d) for the bimodal effect of the brain stress response \( (L_I) \) on the immune response \( (L_I) \). A sensitivity analysis identified \( v_i \) and \( v_b \) and the homeostatic lipolysis rate \( (L_b) \) to a higher therapeutic \( d_p \) (defined in figure 2d) for both the immune response \( (L_I) \) and lipolysis \( (L_b) \) (electronic supplementary material, figure S2A). The impact of \( v_b \) was biphasic (figure 2e), consistent with the existence of an optimal brain stress response for most efficient immunity [48]. The optimal \( v_b \) (figure 2f, magenta, minimum) was modulated by \( L_b \) and \( v_l \) (electronic supplementary material, figure S2C,D). These results suggest that the brain stress response and lipolysis are host parameters critical for pathogen clearance.

Starting from a chronic infection (figure 2f, red, \( d_p = 1.12 \text{ d}^{-1} \)), we investigated the effect of a therapy that boosts the pathogen clearance rate \( (d_p) \) to a higher ‘therapeutic’ \( d_p' \) ( \( d_p' = 1.20 \text{ d}^{-1} \)). An identical therapy resolved the infection when applied from day 5 (figure 2f, blue), but not if applied from day 10 onwards (figure 2f, black). In this example, the critical time to start a successful therapy was 8 days post-infection (figure 2g, dashed black line). The emergence of a critical therapy initiation time is related to dynamic modulation of immune energy usage \( (L_I) \) due to interactions with other network compartments. This critical time was longer for stronger therapies (figure 2g), suggesting that weak therapies must be applied early to ensure pathogen clearance. At a minimal therapeutic strength (figure 2g, blue vertical line), clearance was achieved irrespective of its initiation time (figure 2g) while minimizing (potential) side effects.

For weak regimens, critical therapy initiation time \( (T_c) \) depended on the impact of brain stress on the immune response \( (v_i) \) and \( v_l \) in figure 2f). These two parameters exhibited considerable and opposing impacts on \( T_c \) (figure 2h,i). For strong therapies associated with longer critical times, their impact was negligible and the parameter controlling maximum inhibition of the immune response by brain stress \( (v_i) \) became important (electronic supplementary material, figure S3A). The effect of the homeostatic lipolysis rate \( (L_b) \) (electronic supplementary material, equation S15) was twofold: higher values prolonged the critical time when less than 15 days, and shortened it otherwise (electronic supplementary material, figure S3B). The impact of other host factors on the critical therapy initiation time was small (electronic supplementary material, figure S3C). These results suggest that after 15 days of infection, the organism switches its mode of coping with persistent infections.
Next, we further characterized energy dynamics in response to infections in network compartments. In the course of acute in silico infections (figure 3, blue curves, corresponding to the blue point in figure 2a), energy in blood vessels was transiently upregulated (figure 3b), while energy flow from gut was suppressed (figure 3c), reflecting increased serum levels of fatty acids [49] and anorexia [50] during acute infections, respectively. Energy in the brain was transiently reduced to less than 70% (figure 3d) but recovered after pathogen clearance, corresponding to acute infection-induced sickness behaviour [37].

Although energy in the brain and the immune system showed similar dynamics (figure 3d,e), increased energy inflow and usage was more pronounced and prolonged for the immune response (figure 3g,j) versus liver (figure 3h,k). The inflow of energy into fat tissue was downregulated (figure 3i) while outflow was upregulated (figure 3l), consistent with its role as the energy supplier during infections in a state of acute anorexia [51]. The extent of energy loss in fat tissue (figure 3f) was less than 5%. Recovery was slow (figure 3f, see also figure 2c) and relied on slowly increasing appetite (figure 3c) when brain and immune usage rates returned to normal (figure 3j,k) and their energy content restored (figure 3d,l). The overshoot in energy uptake in gut, brain and immune system at day 10 (figure 3c–e) was required to return to healthy homeostasis. This is also reflected in the fat turnover (figure 3i,l) which compensates loss of fat energy. Overall, the model was consistent with known physiologic dynamics in response to acute infections [52].

In chronic in silico infections (figure 3, red dashed lines, corresponding to the red point in figure 2a), the network was driven into a new homeostatic state—that associated with inflammation. Compared with the healthy state, the diseased state after 175 days of infection was associated with increased energy in the vessel compartment (figure 3b), slightly increased energy inflow from gut (figure 3c), reduced brain and immune system energy (85% of the healthy state; figure 3d,e), and reduced fat energy (75% of the healthy state; figure 3f).

Transition from the acute fight with the pathogen to the state of chronic coexistence was characterized by a rebound in the pathogen load at day 6 (figure 3e; electronic supplementary material, figure S4), concomitant with a transient and attenuated increase of the immune response (figure 3k; electronic supplementary material, figure S4A) and a steady
Figure 3. Model response to acute (blue) or chronic (red) infections. Starting from network equilibrium, pathogen level was raised from 0 to \( P_0 = 1 \) (see electronic supplementary material, equation S3), at day 0. \( d_p = 1.16 \text{ d}^{-1} \) (blue, acute infection) and 1.15 \text{ d}^{-1} \) (red, chronic infection), see blue and red points in figure 2a. All quantities are defined in figure 1 and electronic supplementary material, equations S3–S14, and normalized with respect to their healthy homeostatic levels (rel.). Parameters are given in electronic supplementary material, table S1. The broken time axis indicates long-term behaviour.

decrease in the brain stress response (figure 3j; electronic supplementary material, figure S4B). The relationship between pathogen load and immune response switched around day 18 from a positive to a negative correlation (electronic supplementary material, figure S4A) indicating relative weakness of the immune system after day 18. Energy in the brain and immune system started to recover after day 18 (electronic supplementary material, figure S4C,D), indicating a trade-off between pathogen clearance and organ integrity [53]. By contrast, fat energy decreased continuously before reaching the new disease-related homeostatic state.

2.3. Effects of lipolysis resistance

As the model results identified fat as an important driver of immune responses, we investigated whether modulations of energy flow from fat to blood circulation would impact infection dynamics. We added lipolysis resistance (LR) \( L_r \) to the model (electronic supplementary material, equation S17) [54–57], where release of energy from fat is inhibited for values of \( L_r \) larger than zero. The effects of manually imposed LR are shown in figure 4. For acute infections, inhibition of lipolysis impaired pathogen clearance (figure 4a,b), which was associated with a reduction of fat energy (figure 4c). Sufficient LR turned the acute into a chronic infection.

In the setting of chronic infections, a sufficient inhibition of lipolysis resulted in pathogen clearance (figure 4d,e). The mechanisms underlying this counterintuitive effect, as implied by the model, involved the restoration of the fat compartment due to the orexigenic effect of reduced lipolysis (figure 4f). This beneficial effect of reduced lipolysis was offset by a long-term increase of fat energy associated with obesity [57] (figure 4f), energy deprivation from the brain (figure 4g) and the immune system (figure 4h) as well as high levels of fatty acids in the vessel compartment (figure 4i). These would lead to a deregulated state with impaired bodily functioning and accelerated long-term inflammation [43].

As a manual introduction of LR induced complex dynamics in the model, we next investigated the effects of dynamically regulated LR instead of a stepwise increase. The energy-flow model was extended by including an equation (electronic supplementary material, equation S18) for LR development, where \( L_r \) is driven by immune and stress response with rate \( \alpha \), and decays with rate \( \beta \). The extended model is termed the LR model hereafter.

We investigated the impact of LR on infections by varying the LR growth rate \( \alpha \), while keeping the recovery rate fixed \( (\beta = 0.01 \text{ d}^{-1}) \). For an acute infection (i.e. \( d_p = 1.16 \text{ d}^{-1} \)), low LR growth rates did not change the outcome of the infection (figure 5a, black, left bottom), but the infection duration increased (figure 5a, green) from 10 to 20 days. At the time of pathogen clearance, fat energy decreased and LR increased with \( \alpha \) (figure 5b, black and green, respectively). This suggested the existence of a vicious cycle: a longer infection duration providing more time for LR development, which in turn further impairs lipolysis and prolongs infection. There existed a critical LR growth rate, above which the
3. Discussion

Energy is a dominant force for natural selection during evolution [58]. Immunity is subject to adaptive energy trade-offs during interplay with many physiological functions [20,31,59,60]. Although the idea of energy flow between compartments is a traditional scheme in physics and ecology [61], a comparable modelling approach that associated energy flow with interactions and functions of multiple organs is, to the best of our knowledge, a novel concept. The modelling approach presented here was constructed to describe energy allocation during an immune response to infections in the context of other functional compartments. The trade-offs between energy needs of different compartments emerged at the net-work level and gave rise to known associations of acute and chronic infections with collateral damage to the organism. Thus, we believe that the mathematical model presented in the language of energy flow can potentially explain manifold diseases and their pathogenesis from a transient versus permanent energy shortage in one compartment of the organism and related adaptations of other compartments.

A high pathogen clearance rate, corresponding to an efficient immune response, led to rapid pathogen removal (figure 2b) and subsequent return to healthy homeostasis (figure 2g). Given an extremely efficient immune response,
the synergism arising from interactions with brain and fat tissue (electronic supplementary material, figure S2) would have been negligible and unnecessary. However, optimal protection by the immune system is rarely maximal [62], and higher clearance rates are also more likely to be associated with immunopathology (overshooting immune response and hyperinflammation) [63]. We therefore argue that most of the infections are cleared by a moderate clearance rate such that synergism due to brain and fat activities is crucial to achieve the two competing objectives: minimizing immunopathology and avoidance of chronic infections. In *silico*, chronic infections were associated with long-term low energy in brain and immune system (figure 3), reflecting low performance in other vital functions, such as wakefulness/fatigue and immunocompetence.

The efficiency of the energy-flow system in supporting an immune response was quantified by the critical pathogen clearance rate (\(C_{\text{crit}}\)) that separates acute from chronic infections. If it is low, the pathogen can be cleared by less aggressive immune responses associated with lower immunopathology. The mathematical model suggested that brain and fat tissue regulate the critical clearance rate, thus suggesting interesting targets for medical or behavioural interventions. We speculate that the health benefits associated with intermittent fasting [64] are related to its role in upregulating fat turnover (\(L_{\text{fat}}\)), which reduces the critical clearance rate (figure 2b).

The energy flow model presented here was strictly based on current knowledge of the inter-dependence of organismal compartments. While it also required several assumptions that should be tested in further studies, some simulation results, such as the typical duration of an acute infection (10 days, figure 2a) and fat loss in acute infections (5%, figure 3f), are consistent with common experience.

Further, the energy-flow model predicted that the synergism between the immune system and other tissues gives rise to a critical therapy initiation time, after which a treatment becomes ineffective (figure 2g). It has been recently established in clinical practice that for severe infections, like those of the bloodstream [65], severe bacterial infections [66], or sepsis [67], early instigation of antibiotic therapy (within 13.6 [67], 24 [66] or 48 [65] hours after diagnosis) is associated with reduced mortality. The reason for the observed critical time of antibiotic application will likely involve multi-organ and multi-level mechanisms. The consistency of simulated and clinical observation supports the usefulness of our energy-based perspective and serves to endorse any derived predictions.

The simulations suggested a timeline separating acute from chronic infections at around 18 days for the given parameter values (electronic supplementary material, figure S4). This timeline was also corroborated by the findings that in the context of therapy, the brain stress response was mainly supportive for immune responses before day 15, but suppressive for immune responses thereafter (figure 2h,i). This is in line with the observation that long-term activation of the brain stress axes can be harmful [48]. Interestingly, day 15 coincides with the peak of germinal centre reactions [68]. One might speculate that the emergence of high affinity antibodies as a last resort to fight infections triggers the switch from an elimination to a coexistence strategy.

However, the loss of fat energy appeared to dominate the acute-chronic division, due to its influence on both stress and immune responses. This is further supported by the
predicted role of fat tissue LR or catecholamine resistance, which refers to the phenomenon that the lipolytic response of adipocytes to a sympathetic drive is attenuated [54–56]. This can happen through loss of β2-adrenoceptor signalling [56] or lack of local catecholamines [54,55] and is associated with ageing [55,69] and obesity [57,70]. Contrary to insulin resistance, which is considered a positively selected acute programme to deprive insulin-sensitive organs of energy to support the brain or immune system [71], LR impairs the flow of energy from fat tissue to circulation (the vessel compartment) and subsequently to the brain and immune system. It was anticipated that LR would delay the immune response to infection, which was confirmed by the model results (figure 4a,b and figure 5). However, overcritical inhibition of lipolysis induced clearance of otherwise chronic infection (figure 4d,e and figure 5) by its orexigenic effect. Longstanding LR has been associated with obesity [57] and reduced energy in brain and immune system (figure 4f–h), which may be associated with long-term changes such as inflammation, ageing and neurodegeneration. One might speculate that LR represents an additional layer of energy trade-off that is beneficial over the time scale of years but detrimental over longer periods. The slow regulation of energy release from fat might be critical in the development of chronic disease and aged accelerated ageing.

The mathematical model presented in this paper is subject to several limitations, such as the lack inter alia of a muscle compartment [52,72], daily feeding–fasting cycle and additional feedbacks in the stress response pathway as well as in the immune response pathway. Nevertheless, our energy-flow model enables investigation of the network of subsystems in diseases without the need for the explicit incorporation of complex molecular pathways. It considers the organism as a network of compartments interacting via competition for a limited resource—energy—and promises improved understanding of the mutual interdependence of subsystems as well as the development of new avenues of disease treatment with an eye on the whole organism. We hope these results will stimulate further collaborations between scientists in biology, physics and medicine, thus generating new ideas for the promotion of healthy ageing and disease intervention/management.

**Data accessibility.** The data are provided in electronic supplementary material [73].

**Authors’ contributions.** G.Z.: conceptualization, investigation, methodology, project administration, visualization, writing—original draft; R.H.S.: conceptualization, data curation, methodology, supervision, validation, writing—review and editing; M.M.-H.: conceptualization, funding acquisition, methodology, project administration, supervision, validation, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

**Funding.** G.Z. was supported by the Initiative and Networking Fund of the Helmholtz Association, Zukunftsthema ‘Ageing and Metabolic Programming’ (AMPro), ZT-0026. M.M.-H. is part of Germany’s Excellence Strategy EXC 2155, project 390784280, funded by the German Research Foundation (DFG).

**Acknowledgements.** We thank Dirk Brockmann for valuable comments, and Arnab Bandyopadhyay, Sahamoddin Khailaie and Frank Schlosser for improving the visual presentation of the model structure.

**References**

1. Del Rey A, Besedovsky HO. 2017 Immune-neuro-endocrine reflexes, circuits, and networks: physiologic and evolutionary implications. *Front. Horm. Res.* **48**, 1–18. (doi:10.1159/000452902)

2. Pavlov VA, Chavan SS, Tracey KJ. 2018 Molecular and functional neuroscience in immunity. *Annu. Rev. Immunol.* **36**, 783–812. (doi:10.1146/annurev-immunol-042617-053158)

3. Pluvignage JV, Wyss-Coray T. 2020 Systemic factors as mediators of brain homeostasis, ageing and neurodegeneration. *Nat. Rev. Neurosci.* **21**, 93–102. (doi:10.1038/s41583-019-0255-y)

4. Collins S. 2011 β-Adrenoceptor signaling networks in adipocytes for recruiting stored fat and energy expenditure. *Front. Endocrinol.* **2**, 102. (doi:10.3389/fendo.2011.00102)

5. Kaufmann SA. 1969 Metabolic stability and epigenesis in randomly constructed genetic nets. *J. Theor. Biol.* **22**, 437–467. (doi:10.1016/0022-5193(69)90015-0)

6. Meyer-Herrmann M, Figge MT, Straub RH. 2009 Mathematical modeling of the circadian rhythm of key neuroendocrine-immune system players in rheumatoid arthritis: a systems biology approach. *Arthritis Rheum.* **60**, 2585–2594. (doi:10.1002/art.24797)

7. Ganusov VV, Auerbach J. 2014 Mathematical modeling reveals kinetics of lymphocyte recirculation in the whole organism. *PLoS Comput. Biol.* **10**, e1003586. (doi:10.1371/journal.pcbi.1003586)

8. Anderson WD, DeCicco D, Schwaber JS, Vadigepalli R. 2017 A data-driven modeling approach to identify disease-specific multi-organ networks driving physiological dysregulation. *PLoS Comput. Biol.* **13**, e1005627. (doi:10.1371/journal.pcbi.1005627)

9. Pastor-Satorras R, Vespignani A. 2001 Epidemic spreading in scale-free networks. *Phys. Rev. Lett.* **86**, 3200–3203. (doi:10.1103/PhysRevLett.86.3200)

10. Gawthrop PJ, Crampin EJ. 2014 Energy-based analysis of biochemical cycles using bond graphs. *Proc. R. Soc. Math. Phys. Eng. Sci.* **470**, 20140459. (doi:10.1098/rspa.2014.0459)

11. Lubitz T, Schulz M, Klipp E, Liebermeister W. 2010 Parameter balancing in kinetic models of cell metabolism. *J. Phys. Chem. B* **114**, 16 298–16 303. (doi:10.1021/jp108764b)

12. Liebermeister W, Klipp E. 2006 Bringing metabolic networks to life: convenience rate law and thermodynamic constraints. *Theor. Biol. Med. Model.* **3**, 41. (doi:10.1186/1742-4682-3-41)

13. Cudmore P, Pan M, Gawthrop PJ, Crampin EJ. 2021 Analysing and simulating energy-based models in biology using BondGraphTools. *Eur. Phys. J. E Soft Matter* **44**, 148. (doi:10.1140/epje/i2018-10219-00152-4)

14. Pattaranit R, van den Berg HA. 2008 Mathematical models of energy homeostasis. *J. R. Soc. Interface* **5**, 1119–1135. (doi:10.1098/rsif.2008.0216)

15. Zavala E, Wedgwood KCA, Volleris M, Tabak J, Spiga F, Lightman SL, Tsaneva-Atanasova K. 2019 Mathematical modelling of endocrine systems. *Trends Endocrinol. Metab.* **30**, 244–257. (doi:10.1016/j.tem.2019.01.008)

16. Kurata H. 2021 Virtual metabolic human dynamic model for pathological analysis and therapy design for diabetes. *iScience* **24**, 102101. (doi:10.1016/j.isci.2021.102101)

17. Hall KD, Butte NF, Swinburn BA, Chow CC. 2013 Dynamics of childhood growth and obesity: development and validation of a quantitative mathematical model. *Lancet Diab. Endocrinol.* **1**, 97–105. (doi:10.1016/S2213-8587(13)70051-2)

18. Gao J, Alotaibi FS, Ismail RI. 2021 The model of sugar metabolism and exercise energy expenditure based on fractional linear regression equation. *Appl. Math. Nonlinear Sci.* **6**, 26. (doi:10.2478/amns.2021.2.00026)
21. Furman D et al. 2019 Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* 25, 1822–1832. (doi:10.1038/s41591-019-0675-0)

24. Xie X, Chen W, McDermott J, Han J-DJ. 2017 Molecular and phenotypic biomarkers of aging. *F1000Research* 6, 860. (doi:10.12688/f1000research.10692.1)

25. Straub RH, Dhabhar FS, Bijlsma JWJ, Cutolo M. 2017 Chronic inflammation in immune aging: role of pattern recognition receptor crosstalk with the telomere complex? *Ann. Rheum. Dis.* 86, 157–168. (doi:10.1002/art.20747)

31. Metcalf CJE, Roth O, Graham AL. 2020 Why does biology of inflammation produce catecholamine resistance in T and inflammatory cells? *Front. Endocrinol.* 9, 235. (doi:10.3389/fendo.2018.00225)

32. Straub RH, Dhabhar FS, Bijlsma JWJ, Cutolo M. 2005 How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis. *Arthritis Rheum.* 52, 16–26. (doi:10.1002/art.a1074)

38. Alpert A et al. 2019 A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. *Nat. Med.* 25, 487–495. (doi:10.1038/s41591-019-0381-y)

39. Straub RH, Dhabhar FS, Bijlsma JWJ, Cutolo M. 2017 Inflammation produces catecholamine resistance in T and inflammatory cells. *Front. Endocrinol.* 9, 235. (doi:10.3389/fendo.2018.00225)

40. Blodgett DM, De Zutter JK, Levine KB, Karim P, Carruthers A. 2007 Structural basis of GLUT1 inhibition by cytoplasmic ATP. *J. Gen. Physiol.* 130, 157–168. (doi:10.1085/jgp.200709818)

41. Xiong X-Q, Chen W-W, Zhu G-Q. 2014 Adipose cell afferent reflex: sympathetic activation and obesity hypertension. *Acta Physiol.* 210, 468–478. (doi:10.1111/apha.12182)

42. Sausillo DC, Gerrits VA, Sheng J, Rathmell JC, Madler NA. 2014 Leptin metabolically licenses T cells for activation to link nutrition and immunity. *J. Immunol. (Baltim. Md)* 1950, 192. (doi:10.4049/jimmunol.1301153)

43. Ye J, Keller JN. 2010 Regulation of energy metabolism by inflammation: a feedback response in obesity and calorie restriction. *J. Clin. Invest.* 126, 361–368. (doi:10.1172/JCI41444)

44. Rosenbaum M, Leibel RL. 2014 20 years of leptin: effects of β-adrenergic and cytokine signaling on lipolysis to epinephrine. A new feature of childhood obesity. *J. Clin. Invest.* 125, 2175–2186. (doi:10.1172/JCI71603)

45. Muller K. 1993 Neurophysiological investigative Parameter in der akuten induzierten Hyper- und Hypoglykämie bei stoffwechselgesunden Probanden. Thesis, University Freiberg, Germany.

46. Perry RJ, Wang Y, Cline GW, Rabin-Court A, Song JD, Straub RH. 2019 Lipolysis during ageing. *Nature* 550, 119–123. (doi:10.1038/nature24022)

47. Linnqvist F, Wahrenberg H, Hellstrom L, Reynolds D, Arner P. 1992 Lipolysis in obesity and calorie restriction. *Am. J. Physiol.* 260, E346–E358. (doi:10.1152/ajpendo.1992.260.2.E346)

48. Dhabhar FS. 2014 Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol. Res.* 58, 193–210. (doi:10.1007/s12026-014-8517-0)

49. Grunfeld C, Feingold KR. 1991 Tumor necrosis factor, cytokines, and the hyperlipidemia of infection. *Trends Endocrinol. Metab.* 2, 213–219. (doi:10.1016/1043-2760(91)90027-X)

50. Langhans W. 2000 Anorexia of infection: current prospects. *Nutrition* 16, 996–1005. (doi:10.1016/S0899-9007(00)00421-4)

51. Cumnock K, Gupta AS, Lissner M, Chevee V, Davis NM, Schneider DS. 2018 Host energy source is important for disease tolerance to malaria. *Curr. Biol.* 28, 1635–1642. (doi:10.1016/j.cub.2018.04.009)

52. Friman G, Ilbäck NG. 1998 Acute infection: metabolic responses, effects on performance, interaction with exercise, and myocarditis. *Int. J. Sports Med.* 19.Suppl. 3, S172–S178. (doi:10.1055/s-2007-971990)

53. Rauw WM. 2012 Immune response from a resource allocation perspective. *Front. Genet.* 3, 267. (doi:10.3389/fgene.2012.00267)

54. Mowers J, Uhlen M, Reilly SM, Simon J, Leto D, Chiang S-H, Chang L, Saltiel AR. 2013 Inflammation produces catecholamine resistance in obesity via activation of PDE8B by the protein kinases IKKe and TBK1. *eLife* 2, e01119. (doi:10.7554/eLife.01119)

55. Camell CD et al. 2017 Inflammation-associated catecholamine catabolism in macrophages blunts lipolysis during ageing. *Nature* 550, 119–123. (doi:10.1038/nature24022)

56. Lambris JD, Wahrenberg H, Hellstrom L, Reynolds D, Arner P. 1992 Lipolysis in obesity and calorie restriction. *Am. J. Physiol.* 260, E346–E358. (doi:10.1152/ajpendo.1992.260.2.E346)

57. Lane N, Martin WF, Raven JA, Allen JF. 2013 Energy, genes and evolution: introduction to an evolutionary synthesis. *Phyl. Trans. R. Soc. B* 368, 20120253. (doi:10.1098/rstb.2012.0253)

58. Lochmüller RL, Deerenberg C. 2000 Trade-offs in evolutionary immunity: just what is the cost of immunity? *Oikos* 88, 87–98. (doi:10.1034/j.1600-0706.2000.880110.x)

59. Ganesan K et al. 2019 Energetic trade-offs and hypometabolic states promote disease tolerance. *Cell* 177, 399–413. (doi:10.1016/j.cell.2019.01.050)

60. Lindeman RL. 1942 The trophic-dynamic aspect of energetic trade-offs and depression: when the immune system illuminates the evolution of senescence. *Ecol. Monogr.* 17, 217–218. (doi:10.2307/1930126)

61. Cressler CE, Graham AL, Day T. 2015 Evolution of hosts paying manifold costs of defence. *Proc. R. Soc. B* 282, 20150065. (doi:10.1098/rspb.2015.0065)

62. Sorci G, Lippens C, Léchenault C, Faivre B. 2017 Benefits of immune protection versus immunopathology costs: a synthesis from cytokine NK models. *Infect. Genet. Evol.* 54, 491–495. (doi:10.1016/j.meegid.2017.08.014)

63. Mindkougou AL et al. 2020 Intermittent fasting from dawn to sunset for 30 consecutive days is associated with anticancer proteomic signature and upregulates...
key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodeling, immune system and cognitive function in healthy subjects. J. Proteomics 217, 103645. (doi:10.1016/j.jprot.2020.103645)

65. Robineau O, Robert J, Rabaud C, Bedos J-P, Varon E, Péan Y, Gauzit R, Alfandari S. 2018 Management and outcome of bloodstream infections: a prospective survey in 121 French hospitals (SPA-BACT survey). Infect. Drug Resist. 11, 1359–1368. (doi:10.2147/IDR.S165877)

66. Falcone M et al. 2020 Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit. Care 24, 29. (doi:10.1186/s13054-020-2742-9)

67. Li Q et al. 2019 Effects of delayed antibiotic therapy on outcomes in children with Streptococcus pneumoniae sepsis. Antimicrob. Agents Chemother. 63, e00623-19. (doi:10.1128/AAC.00623-19)

68. MacLennan IC. 1994 Germinal centers. Annu. Rev. Immunol. 12, 117–139. (doi:10.1146/annurev.iy.12.040194.001001)

69. Camell CD et al. 2019 Aging induces an Nlrp3 inflammasome-dependent expansion of adipose B cells that impairs metabolic homeostasis. Cell Metab. 30, 1024–1039. (doi:10.1016/j.cmet.2019.10.006)

70. Pirzgalska RM et al. 2017 Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine. Nat. Med. 23, 1309–1318. (doi:10.1038/nm.4422)

71. Straub RH. 2014 Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases. Arthritis Res. Ther. 16, 54. (doi:10.1186/ar4688)

72. Liu Z, Shao H, Alahmadi D. 2021 Numerical calculation and study of differential equations of muscle movement velocity based on martial articulation body ligament tension. Appl. Math. Nonlinear Sci. (doi:10.2478/amns.2021.1.00051)

73. Zhao G, Straub RH, Meyer-Hermann M. 2022 The transition between acute and chronic infections in light of energy control: a mathematical model of energy flow in response to infection. Figshare. (doi:10.6084/m9.figshare.c.6016899)