Viable flux distribution in metabolic networks

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\textbf{Summary.} The metabolic networks are very well characterized for a large set of organisms, a unique case in within the large-scale biological networks. For this reason they provide a very interesting framework for the construction of analytically tractable statistical mechanics models. In this paper we introduce a solvable model for the distribution of fluxes in the metabolic network. We show that the effect of the topology on the distribution of fluxes is to allow for large fluctuations of their values, a fact that should have implications on the robustness of the system.

1 Introduction

Dynamical models on networks have attracted a large interest because of the non-trivial effects of network structure \cite{1, 2, 3, 4} on the dynamics defined on them \cite{5}. Important examples of the dynamics on networks with relevant applications are the Ising model \cite{6, 7, 8}, the spreading of a disease \cite{9} and the synchronization models \cite{10, 11}. In this paper introduce a solvable model for the distribution of fluxes in the metabolic network. While motivations come from the study of the metabolic network, the problem is quite general and can be applied to supply networks and to many other linear problems \cite{12} of constraint satisfaction on continuous variables on a network.

Metabolic networks describe the stoichiometric relations between substrates in biochemical reactions inside the cell. They have been mapped \cite{13} for a large number of organisms in the three different domains of life (archaea, bacteria and eukaryotes). They provide the biomass needed for cell duplication, and the rate of biomass production (growth rate) can be identified with a fitness of the cell. The structure of the metabolic network can be represented as a factor graph with nodes that are chemical reactions and function nodes that are chemical metabolites. The projection of the network on the metabolites has a power-law degree distribution and a hierarchical structure \cite{14, 15, 16}. To each factor node, which describes a chemical reactions, it is associated an enzyme which itself is produced by a regulated gene network.
Important aspect of the functioning of these very complex systems include
dynamical considerations. Flux-balance-analysis \[17, 18, 19\] make a major
simplification in the problem. In fact it considers only the steady state of the
dynamics and includes all the dynamical terms inside the definition of the flux
of a reaction. For this reason it was able to predict with sufficient accuracy
the fluxes of the reactions in the graph for a given environment and it con-
stitute a real break-through in the field. Special interest has been addressed
to the perturbation of the distribution of the fluxes after knockout of a gene
or in different environments \[20, 21\]. The problem of identifying the flux dis-
tribution in \textit{Escherichia coli} was studied experimentally \[22\] and by means
of Flux-Balance-Analysis \[23\]. A fat tail in their distribution with different
power-law exponents \(\alpha < 2\) was found.

Metabolic networks provide a very interesting framework for the construc-
tion of analytically tractable models using tools of statistical mechanics of
disordered systems. In this paper we will discuss the impact of the network
structure (degree distributions) on the steady state distribution distribution
of the fluxes. We shall consider random networks with the same degree dis-
tribution as the real ones i.e. networks in the the hidden-variable ensemble
\[24, 25, 26\] with same expected degree distribution as the metabolic factor
graphs. Formally the problem is resolved with replica calculations on diluted
networks \[7\] extended to the case of continuous variables. Due the simplicity
of the Hamiltonian the problem is solved with an expansion of the order pa-
rameter in terms of Gaussians. The problem shares some similarity with other
problems in statistical mechanics of disordered systems \[28, 29\]. In a recent
paper \[30\] a similar problem was considered in the framework of a different
model where the steady state of the fluxes is not a priori considered and the
positive fluxes don’t have any upper limit.

2 The model

The metabolic network has a bow tie structure \[16\] : the metabolites are
divided into: (i) input metabolites which are provided by the environment, (ii)
the output metabolites which provide the biomass and (iii) the intermediate
metabolites. The stochiometric matrix is given by \((\xi_{\mu,i})\) where \(\mu = 1, \ldots, M\)
indicates the metabolite and \(i = 1, \ldots, N\) the reaction and the sign of \(\xi_{\mu,i}\)
indicates if the metabolite \(\mu\) is an input or output metabolite of the reaction
\(i\). As in the Flux-Balance-Analysis method we assume that each intermediate
metabolite has a concentration \(c_\mu\) which is consumed/produced by a reaction
\(i\) at a rate \(f_i\). At steady state, we have

\[
\frac{dc_\mu}{dt} = \sum_i \xi_{\mu,i} f_i = a^\mu = 0
\]

where \(f_i\) is the flux of the metabolic reaction \(i\). For the metabolites present
in the environment and the metabolites giving rise to the biomass production

we can fix the incoming flux given by
\[ \frac{dc_\mu}{dt} = \sum_i \xi_{\mu,i} f_i = a^{\mu}_{\text{in/out}}. \] (2)

The fluxes in Eqs.(1-2) can vary inside a fixed volume \( \Omega \). We assume for simplicity that this volume is a hypercube \( \Omega = [0, 2L]^N \). Changing the variables \( f_i \) in the variables \( s_i = f_i - L \) and the equations that the fluxes \( s_i \) must satisfy are given by
\[ \sum_{i=1}^{N} \xi_{\mu,i} s_i = g_\mu \quad \text{for} \quad \mu = 1, \ldots, M. \] (3)
where \( g_\mu = a^\mu - L \sum_i \xi_{\mu,i} \). The volume of solutions \( V \), given the constraints (3), is proportional to the quantity
\[ \tilde{V} = \int_0^L dL' \prod_{i=1}^{N} ds_i \delta(\sum_{i} \xi_{\mu,i} s_i - g^\mu) \delta(\sum_j q_j s_j^2 - \langle q_i \rangle NL^2). \] (4)
where we have used the heterogeneous spherical constraints
\[ \frac{1}{\langle q_i \rangle N} \sum_i q_i s_i^2 = L^2 \] (5)
and integrated over \( L' \) in the interval \([0, L]\) in order to allow analytical treatment of the problem.

3 Replica method

We assume that the support of our stochiometric matrix is a random network with given degree distribution, i.e. a realization of the random hidden-variable model [24, 25, 26]. In particular we fix the expected degree distribution of the nodes of the factor graphs to be \( q_i \) for the reaction node \( i = 1, \ldots, N \) and \( q_\mu \) for the metabolite nodes \( \mu = 1, \ldots, M \) and we assume that the matrix elements \( \xi_{\mu,i} \) are distributed following
\[ P(\xi_{\mu,i}) = \frac{q_\mu q_i}{2\langle q_i \rangle N} \left[ \delta(\xi_{\mu,i} - 1) + \delta(\xi_{\mu,i} + 1) \right] + \left( 1 - \frac{q_\mu q_i}{\langle q_i \rangle N} \right) \delta(\xi_{\mu,i}), \] (6)
where \( \delta() \) indicates the Kronecker delta. Note that in (6) we have assumed that the elements of the stochiometric matrix have values 0, ±1 with a random sign and that the variables \( q_i, q_\mu \) are nothing else than the hidden-variables associated with metabolite \( \mu \) of the reaction \( i \) of the hidden-variable network ensemble [24, 25, 26].

In order to evaluate the steady state distribution of the fluxes in a typical network realization we replicate the realizations of the \( s_i^a \) and we compute
\( \langle \log(V) \rangle \) over the different network realizations. To calculate this average we use the replica trick \( S = \langle \log(Z) \rangle = \lim_{n \to 0} \frac{\langle V^n \rangle - 1}{n} \). The averaged unnormalized volume of solutions \( < \hat{V}^n > \) can be expressed as

\[
< \hat{V}^n > = \int_0^L dL' \int \prod_a d\omega^a \int \prod_i ds_{i,a} \int \prod_{a,\mu} d\lambda_{\mu,a} \exp \left[ -ig_{\mu} \sum_a \lambda_{\mu,a} \right] \\
\exp \left[ -\sum_{i,\mu} \frac{q_i g_{\mu}}{(q_i)^N} (1 - \cos \lambda_{\mu} \cdot s_i) + i \sum_a \omega^a \left( \sum_j q_j s_{j,a}^2 - L^2 \langle q_i\rangle N \right) \right]. \tag{7}
\]

Using the techniques coming from the field of diluted systems, we introduce the order parameters \([31, 7]\)

\[
c(\lambda) = \frac{1}{\langle q_i\rangle N} \sum_{\mu} q^\mu \prod_a \delta(\lambda^a_{\mu} - \lambda^a) \\
c(s) = \frac{1}{\langle q_i\rangle N} \sum_i q^i \prod_a \delta(s_i^a - s^a) \tag{8}
\]

getting for the volume

\[
\langle \hat{V}^n \rangle = \int Dc(\lambda) \int D\hat{c}(\lambda) \int Dc(s) \int D\hat{c}(s) \exp[n\Sigma(c(\lambda), \hat{c}(\lambda), c(s), \hat{c}(s))]
\]

with

\[
n\Sigma = \int d\lambda i\hat{c}(\lambda)c(\lambda) + \int ds i\hat{c}(s)c(s) - \int d\lambda \int dc(\lambda)c(s)(1 - \cos(\lambda \cdot s)) + \\
+ \frac{1}{\langle q_i\rangle N} \sum_{\mu} \log \int d\lambda \exp[-ig_{\mu} \sum_a \lambda_{a} - iq_{\mu} \hat{c}(\lambda)] - i \sum_a \omega^a L^2 \\
+ \frac{1}{\langle q_i\rangle N} \sum_i \log \int ds \exp[-iq_is(s) + i \sum_a q_i \omega_a s^a_2].
\]

The saddle point equations for evaluating \( \Sigma \) are given by

\[
i\hat{c}(\lambda) = \int dc(s)(1 - \cos(\lambda \cdot s)) \\
i\hat{c}(s) = \int d\lambda c(\lambda)(1 - \cos(\lambda \cdot s)) \\
c(\lambda) = \frac{1}{\langle q_i\rangle N} \sum_{\mu} q^\mu \prod_a \exp[ -ig_{\mu} \sum_a \lambda_{a} - iq_{\mu} \hat{c}(\lambda)] \\
c(s) = \frac{1}{\langle q_i\rangle N} \sum_i q^i \prod_a \exp[ -iq_i \hat{c}(s) + i \sum_a \omega_a s^2_a] \\
L^2 = \frac{1}{\langle q_i\rangle N} \sum_i q^i \frac{\int ds s^2 a \exp[-iq_i \hat{c}(s) + i \sum_a q_i \omega_a s^2_a]}{\int ds' \exp[-iq_i \hat{c}(s) + i \sum_a q_i \omega_a s^2_a]}. \tag{9}
\]
We assume that the solution of the saddle point equation is replica symmetric, i.e. the distribution of the variables $z^a = \lambda^a, s^a$ conditioned to a vector field $x$ are identically equal distributed, 

$$c(z) = \int dx P(x) \prod_{a=1}^{n} \phi(z^a|x)$$

(10)

where $\phi(z|x)$ are distribution functions of $z$ and $P(x)$ is a probability distribution of the vector field $x$. For the function $\phi(z|x)$ the exponential form is usually assumed in Ising models. In our continuous variable case for our quadratic problem, we assume instead that $\phi(z|x)$ has a Gaussian form. This assumption could be in general considered as an approximate solution of the equations (9). Explicitly we assume that the functions $c(\lambda)$ and $c(s)$ can be expressed as the following,

$$c(\lambda) = \int dm_\lambda dh_\lambda P(h_\lambda, m_\lambda) \prod_a \exp \left[ -\frac{1}{2} h_\lambda \lambda_a^2 + \frac{1}{2} m_\lambda^2 \right] \cos[m_\lambda \lambda_a] \sqrt{\frac{h_\lambda}{2\pi}}$$

$$c(s) = \int dm_s dh_s P(h_s, m_s) \prod_a \exp \left[ -\frac{1}{2} h_s s_a^2 - \frac{1}{2} m_s^2 \right] \cosh[m_s s_a] \sqrt{\frac{h_s}{2\pi}}$$

$$\omega_a = i \omega$$

(11)

from which we derive for $\hat{c}(s)$ and $\hat{c}(\lambda)$

$$\hat{c}(s) = -i \left( 1 - \int dm_\lambda dh_\lambda P(h_\lambda, m_\lambda) \prod_a \exp \left[ -\frac{1}{2} h_\lambda \lambda_a^2 \right] \cosh[m_\lambda \lambda_a] / h_\lambda \right)$$

$$\hat{c}(\lambda) = -i \left( 1 - \int dm_s dh_s P(h_s, m_s) \prod_a \exp \left[ -\frac{1}{2} h_s \lambda_a^2 \right] \cos[m_s \lambda_a / h_s] \right)$$

(12)

The saddle point equations (9), taking into account the expression for the order parameters (11)(12) closes and can be written as recursive equation for $P(h_\lambda, m_\lambda)$ and $P(h_s, m_s)$, i.e.

$$P(h_\lambda, m_\lambda) = \frac{1}{(q_t)^N} \sum_{\mu} \sum_k q_\mu e^{-q_\mu} \frac{1}{k!} \left( \prod_i \int dh_i^s dm_i^s \right) P(h_i^s, m_i^s)$$

$$P(h_\lambda, m_\lambda) = \delta \left( h_\lambda - \sum_{i=1}^{k} \frac{1}{h_i^s} \right) \frac{1}{2^k} \sum_{\{n_i\}} \delta \left( m_\lambda - \sum_{i} (-1)^{n_i} \frac{m_i^s}{h_i^s} - g_\mu \right)$$

$$P(h_s, m_s) = \frac{1}{(q_t)^N} \sum_i q_i e^{-q_i} \frac{1}{k!} \left( \prod_i \int dh_i^s dm_i^s \right) P(h_i^s, m_i^s)$$

$$P(h_s, m_s) = \delta \left( h_s - \sum_{i=1}^{k} \frac{1}{h_i^s} - 2\omega q_i \right) \frac{1}{2^k} \sum_{\{n_i\}} \delta \left( m_s - \sum_{i} (-1)^{n_i} \frac{m_i^s}{h_i^s} \right)$$

(13)
\[
L^2 = \frac{1}{\langle q_i \rangle^N} \sum_i q_i e^{-q_i} \left( \sum_k \frac{q_i^k}{k!} \sum_s q_i^s \frac{1}{2^k} \int \prod_i dh_i^s dm_i^s \prod_i P(h_i^s, m_i^s) \right)
\]

\[
\frac{(H + M^2)}{\delta} \left( H - \sum_{i=1}^k \frac{1}{h_i^\lambda} - 2\omega q_i \right) \frac{1}{2^k} \sum_{(n_i)} \delta \left( M - \sum_i (-1)^{n_i} \frac{m_i^\lambda}{h_i^\lambda} \right).
\]

Finally, \( S \) can be calculated at the saddle point as

\[
S = -\int dh_s dm_s dh_\lambda dm_\lambda P(h_s, m_s) P(h_\lambda, m_\lambda) \left[ \frac{\left( m_s / h_s \right)^2}{2(h_\lambda + 1 / h_s)} + \frac{(m_\lambda / h_\lambda)^2}{h_s + 1 / h_\lambda} + \log \cosh \left( \frac{m_s m_\lambda}{h_s h_\lambda + 1} \right) \right] + \\
+ \frac{1}{\langle q_i \rangle^N} \sum_i \sum_k \frac{e^{-q_i q_i^k}}{k!} \prod_i dh_i^s dm_i^s P(h_i^s, m_i^s) \frac{1}{2^{k+2}} \left[ \frac{g_\mu + \sum_i (m_{s,i} / h_{s,i})^2}{\sum_j \kappa_{j,s} + 2\omega q_i} \right] + \\
+ \frac{1}{\langle q_i \rangle^N} \sum_i \sum_k \frac{e^{-q_i q_i^k}}{k!} \prod_i dh_i^\lambda dm_i^\lambda P(h_i^\lambda, m_i^\lambda) \frac{1}{2^{k+1}} \left[ \frac{\sum_i (m_{\lambda,i} / h_{\lambda,i})^2}{\sum_i \kappa_{i,\lambda} + 2\omega q_i} \right]
\]

4 Population Dynamics

We solved the equations (13) by a population-dynamical algorithm. We represent the effective field distributions \((h_s, m_s) (h_\lambda, m_\lambda)\) by a large population of \(P \gg 1\) fields. Running the algorithm the population is first initialized randomly and then equations (13) are used to iteratively replace the fields inside the population until convergence is reached. Instead of fixing \(\omega\) we introduce a further variable \(\Lambda\) fixing the value of the average flux in the network. The action of the algorithm is summarized in the following pseudo code

\textbf{algorithm} PopDyn(\(\{h_1^s, m_1^s, h_2^s, m_2^s, \ldots, h_s^P, m_s^P\}; \)

\(\{h_1^\lambda, m_1^\lambda, h_2^\lambda, m_2^\lambda, \ldots, h_\lambda^P, m_\lambda^P\}, \omega\))

\textbf{begin}

\textbullet\ choose a metabolite \(i_0\) with probability \(q_i P(q_i)\);

\textbullet\ draw \(d\) from a Poisson distribution \((e^{-q_i} q_i^k / k!)\)

\textbullet\ select \(d\) indexes \(i_1, \ldots, i_d \in \{1, \ldots, M\}\)

\textbullet\ draw a \(d\)-dimensional vector \(n = \{n_i\}\) of random numbers \(n_i = 0, 1\)
\[ h^{io}_s := \frac{1}{h^\mu_\lambda} + 2\omega q_i; \]

\[ m^{io}_s := \sum_{i=1}^d (-1)^{m_i^i} \frac{m_i^i}{h^\mu_\lambda}; \]

\[ L_2 := \left( 1 - \frac{1}{\langle q^i \rangle N} \right) L_2 + \frac{1}{\langle q_i \rangle N} \frac{h_s^{io} + (m_s^{io})^2}{(h_s^{io})^2}; \]

\[ \omega := \frac{L_2}{A^2} \]

\( (15) \)

- choose a random reaction \( \mu_0 \) with probability \( q_\mu P(q_\mu) \)
- draw \( d \) form a Poisson distribution \( (e^{-q_\mu q_\mu^k} / k!) \)
- select \( d \) indexes \( i_1, \ldots, i_d \in \{1, \ldots, M\} \)
- draw a \( d \)-dimensional vector \( n = \{n_i\} \) of random numbers \( n_i = 0, 1 \)

\[ h^{\mu_0}_\lambda := \sum_{i=1}^d \frac{1}{h^\mu_s} + 2\omega; \]

\[ m^{\mu_0}_\lambda := \sum_{i=1}^d (-1)^{m_i^i} \frac{m_i^i}{h^\mu_s} + g^{\mu_0} \]

\( (16) \)

while (not converged)

return

end

We run the population dynamics algorithm and we measure the distribution of the average fluxes \( m_s/h_s \), the distribution of the fields \( h_s \) for different values of \( \Lambda \). We consider as the underline network a network with the real degree distribution of the metabolic factor graph of Saccharomyces cerevisiae and on a network with the same number of metabolites and reactions as the real Saccharomyces cerevisiae network but with a fixed connectivity for each metabolite and reaction node. We consider a population of \( P = 3000 \) pair of fields \( (h_s, m_s) \). A random fraction of 5% of the nodes is chosen as an input/output metabolite. The values of \( g^\mu \) are chosen randomly depending if the metabolite \( \mu \) is an intermediate metabolite or an input/output metabolite.

For the input/output metabolites we assume that \( g^\mu \) is a random number uniformly distributed in the interval \([-100\Lambda, 100\Lambda]\) mimicking high rate of production/consumption. For intermediate metabolites we choose \( g^\mu \) with a uniform distribution in the interval \([-\Lambda, \Lambda]\).
The distribution of \( m_s/h_s \) as a function of \( \Lambda \) are plotted in figure 1(a) for the real metabolic network of *Saccharomyces cerevisiae* and in figure 1(b) for the random network with two delta function degree distribution \( P(q_i) = \langle q_i \rangle \), \( P(q_i) = \langle q_i \rangle N/M \). We observe that the average fluxes distribution \( m_s/h_s \) in *Saccharomyces cerevisiae* for low \( \Lambda \) has a fatter tail for the real degree distribution than for the two delta peak degree distribution.

On the other side the distribution of \( h_s \) is very different in the real and in the random case (see figure 1(c)-(d)). In particular for the real metabolic network degree distribution is broader allowing with higher probability for smaller value of \( h_s \) than in the case of a two delta peak degree distribution. Therefore we have shown that the real topology of the networks has as a major consequence in allowing larger fluctuations of the fluxes in the network.

**Fig. 1.** Distribution of the fields \( m_s/h_s \) and of the fields \( h_s \) for a the real degree distribution of the metabolic network of *Saccharomyces cerevisiae* (graphs (a) and (c))and for a graph with the same number of metabolites and reactions and the same number of nodes that the real metabolic network of *Saccharomyces cerevisiae* but with two delta peaks for the degree distribution (graphs (b) and (d)).

5 Conclusions

In this paper we have proposed a statistical mechanics approach for the study of flux-balance-analysis in a particular ensemble of metabolic networks. We
have studied the impact of the topology of the networks on the distribution of the fluxes. We observe that the role of the real topological structure is to allow for larger variation of the fluxes, a fact that should have implications for the robustness of the system. In particular we found that the topology of real metabolites has an impact on the fat tail of the \( m_s/h_s \) distribution and on the small \( h \) field of the network. Further work is under consideration for the implementation of a message-passing algorithm able to predict the fluxes taking into account the full complexity of the real metabolic network.

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