Towards Inverse Modeling of Intratumor Heterogeneity

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Development of resistance limits efficiency of present anticancer therapies and preventing it remains big challenge in cancer research. It is accepted, at intuitive level, that the resistance emerges as a consequence of cancer cells heterogeneity at molecular, genetic and cellular levels. At the same time, population heterogeneity stands as one of fundamental prerequisite of evolutionary theory, which was accepted long time ago as an instructive conceptual framework to understand cancer behavior. Produced by many sources, tumor heterogeneity is extremely complex time dependent statistical characteristics which may be quantified by the measures defined in many different ways, most of them coming from statistical mechanics. While genetic intratumor diversity is well accepted as necessary prerequisite of evolution, the role of non-genetic intratumor diversity in cancer progression is not yet satisfactorily explained. In the paper we present a formal framework to analyze intratumor heterogeneity respecting evolutionary causation of cancer. The approach is based on the concept of master equation, successfully applied in the domain of statistical physics.

I. INTRODUCTION

Intratumor heterogeneity (ITH), referring to biological differences between malignant cells within the same tumor, is considered to be a major obstacle in successfully eradicating tumors [1]. While normal cells respond very similarly to drugs, mechanisms of resistance of cancer cells are extremely diverse [2, 3], which poses real challenge for targeted cancer therapies. Therefore, the development of novel effective cancer treatment strategies requires deep understanding causes and consequences of high variability of cancer cells.

Cancer research usually concentrates on molecular details, implicitly presuming predominance of determinism in cancer causation. Taking into account that ITH results from specifically altered biochemical interactions of the cells with their environment [4, 5], the effort to understand its biochemical basis with the perspective of its therapeutic application is understandable. On the other hand, ITH represents by definition collective property of cells population and its role is conceived with difficulty from the single-cell viewpoint. It implies necessity to take the statistical aspect of cancer progression into account using the concepts of statistical mechanics and/or information theory. The recognition that stochasticity of molecular processes induces heterogeneity of responses to drugs, which may have clinical impact even in the case of genetically identical cells under identical physical conditions [6], underlines necessity to integrate stochastic aspect of cancer progression into cancer models.

Genetic component of ITH is well understood as necessary prerequisite of cancer evolution. Nature selects for phenotype, not genotype, and it is recognized that common phenotypes, cancer as well as normal, can have myriad genetic causes [7]. On the other hand, emerging evidence supports the view, that the ability of cancer cells to switch between alternative states (or phenotypes) without the change of their genotype, i.e. their plasticity, may be essential in many cancer types [8]. The role of this non-genetic part of ITH in cancer progression is, however, from evolutionary viewpoint less obvious. The evidence accumulates, that dynamic and reversible phenotype plasticity may constitute an "escape route" for cancer cells which may become more invasive and resistant to therapy [9].

In the paper we presume, that statistics of ITH plays in cancer initiation and progression important role per se and may be studied separately from underlying it biochemistry. Composed of the two components, genetic and non-genetic, ITH becomes extremely complex statistical quantity which may be quantified by different measures, most of them coming from statistical mechanics, e.g. entropy concept [10–12]. Instead of trying to be (too) detailed in some of the aspects, we put the emphasis on the integration of the universal evolutionary features into the overall scenario. Applied Markovian-based framework enables to study universal causative role of environmental dynamics on the heterogeneity of the population of asexually reproducing units ("cells"). Cell states heterogeneity is bound with environmental statistics by making transition probabilities dependent on generalized distances between probability distribution functions corresponding to environment and the cell states, respectively. Transforming ITH into a tractable and computable property of the population of cells provides a rigorous starting point for developing mathematical cancer models and simulations [13].
II. MASTER EQUATIONS FOR TRANSITION PROBABILITIES

Many physical systems may be represented by a dynamic model in which the system is, at any given time, exactly in one of discrete number of states \( \{1, 2, \ldots, N\} \), and where switching between states is treated probabilistically. Assume that the continuous time variation of the probability obeys well known first-order phenomenological master equation

\[
\frac{dp_i}{dt} = \sum_{k=1}^{N} W_{ki} p_k - \sum_{k=1}^{N} W_{ik} p_i, \tag{1}
\]

where \( p_i(t), i = 1, 2, \ldots, N \), are probabilities that the system is in the \( i \)-th state and \( W_{ki}, k = 1, 2, \ldots, N \) are transition probabilities \( k \)-th to the \( i \)-th state per unit time. The underlying principle of the above equation, stating that appropriate constant transition probabilities may produce physically correct stationary distributions, has been exploited in the design of Monte Carlo importance sampling simulation techniques \cite{14}. When \( W_{ki} \) is constant, the process of interstate switching is Markovian, but when \( W_{ki}(t) \) depends on the actual time \( t \), the process becomes non-stationary.

It was reported, that tumor propagating cells are maintained by, at least partially, reversible mechanisms which are stochastic rather than deterministic \cite{15–20}. It was found \cite{21}, that the only population of human breast cancer cells consists of three phenotypically different sub-populations (consisting of stem, basal and luminal cells, respectively). Studying dynamics of the cell-types fractions it was found, that these stay under stationary conditions in equilibrium proportions \cite{21}. Moreover, if cancer cells population was purified for any of the three cell types, the equilibrium was re-established too rapidly to be explained by differential growth rates of the respective cell-types fractions. Therefore, it was proposed, that phenotypic equilibrium was caused by stochastic transitions between different cell states instead and that under fixed genetic and environmental conditions are the transition rates per unit time constant. Consequent Markovian model \cite{21} implicitly links equilibrium phenotypic heterogeneity with limiting distribution of states of the respective Markovian process.

Identification of the cell-state dynamics with Markovian process enables to study statistical aspects of population dynamics separately from the details of underlying it biochemistry, which stay hidden in the probabilities of transitions between states. Despite the fact, that biochemical processes beyond the respective transitions are very probably interdependent, huge complexity of the problem leaves the opportunity to get, in principle, any equilibrium distribution of the cell states by many alternative transition matrices. Consistently with this, many paths and mechanisms of transitions between cell states (‘phenotype switching’) are observed at molecular, genetic and expression levels \cite{22 26} and theoretically studied \cite{24 54}.

Below we apply time-continuous differential master equation \( \text{(1)} \) to develop more flexible model for further theoretical analysis. On the one hand, it preserves Markovian property, on the other hand, it enables to study non-equilibrium phenomena which reflect the temporal variability of the environment. Assuming that evolving system is, at cancer-relevant time scales, influenced by the variable environment, we focus on the inherent structure of time-dependent \( W_{ki}(t) \) at phenomenological level. Moreover, we consider more profound dependence of \( W_{ki} \) on the specific distance measures of states distributions. It should be emphasized, that the term ‘distance’ is understood here in its broad mathematical meaning, as a distance between two probability distributions. The reason for this specific formalism is two-fold. First, phenotypic distributions of cell populations are typical outputs of flow cytometry experiments \cite{16}. Secondly, in the dynamic system conceptualization, the cell states were epitomized by the respective attractors distributed around stable states in epigenetic landscape \cite{32}.

In here proposed approach we express the transition matrix in the terms of generalized distances between the pairs of probability density functions corresponding to environment and the attractors. Our phenomenological model postulates, that transitions are associated with matching conditions of the attractor distributions comprised in

\[
W_{ij} = C \exp(\alpha(f_j - f_i)) \exp(-\lambda d_{ij}^2), \tag{2}
\]

where \( f_i \) expresses the measure of attractivity of the \( i \)-th attractor under instant environmental factors and \( \alpha \) is an amplitude parameter determining relative strength of this environmental influence. The second term, \( \exp(-\lambda d_{ij}^2) \), manifests dependence of the transition probability on the generalized distance, \( d_{ij} \), between the attractors \( i \) and \( j \). The distance appears in \( \text{(2)} \) in squared form in analogy with the transition term for diffusion of random walk process. In this context \( \lambda \) parameter represents reciprocal value of the diffusion coefficient.

The constant \( C \) simply stems from the normalization condition

\[
\sum_{j=1}^{N} W_{ij} = \frac{1}{\tau}, \tag{3}
\]

where \( \tau \) is the specific time scale of the transitions. The parameter is assumed to be much smaller than the evolutionary time scale. Then the normalized form of \( W_{ij} \) may be written as

\[
W_{ij} = \frac{1}{\tau} \frac{\exp(\alpha f_j - \lambda d_{ij}^2)}{\sum_{s=1}^{N} \exp(\alpha f_s - \lambda d_{is}^2)}. \tag{4}
\]
Suppose, that the probability density function of the above environmental factors of interest is parametrized by the single parameter or parameters comprised in \( \theta^e \). Similarly, the probability density function associated with the \( i \)-th attractor is parametrized by \( \theta_i, i = 1, 2, \ldots, N \). The impact of the \( i \)-th attractor is proportional to the generalized distance of \( \theta_i \) from the current probability distribution which reflects environmental conditions expressed by \( \theta^e \). To sum up, the effect of environment may be quantified by a squared generalized distance \( d^2(\theta_i, \theta^e(t)) \), normalized, without the loss of generality, to interval ranging from 0 to 1. This tendency is captured by the phenomenological equation

\[
f_i(t) = f_A \left( 1 - d^2(\theta_i, \theta^e(t)) \right),
\]

where \( f_A > 0 \) is the amplitude common to all attractors. According to the above equation, more accurate matching with environment represents higher comparative advantage. Within the above biological context, \( \theta_i \) is assumed to be fixed (being already evolved), while the parameters of the environment \( \theta^e(t) \) are allowed to vary. After the substitutions, \( W_{ij} \) can be simply rewritten into the following form

\[
W_{ij}(t, \{\theta_i\}_{i=1}^N, \theta^e(t)) = \frac{1}{\sum_{s=1}^N \exp \left[ -\beta d^2(\theta_j, \theta^e(t)) - \lambda d^2(\theta_i, \theta_j) \right]} \exp \left[ -\beta d^2(\theta_j, \theta^e(t)) - \lambda d^2(\theta_i, \theta_j) \right],
\]

where new parameter \( \beta \) replaces the product \( \alpha f_A \).

Regarding the cause of the state transitions, these are often classified according to whether they occur as a direct response to environmental cue (resonant switching), or without direct sensing of environment (stochastic switching) \[33\]. Within context of the above classification, the parameters comprised in Eq.\[6\] may be interpreted as follows. The parameter \( \beta \) express dependence of the transition probabilities on instant environment and corresponds to resonant switching, and \( \lambda \) is related to the probability of switching. The constants \( \beta, \lambda \) stem purely from genetic basis which was fixed during long evolutionary history.

Being demonstrated, that population of breast cancer cells purified for one of the stable cell types converges in stationary conditions to original (equilibrium) phenotypic fractions \[21\] put in question exclusivity of sensing mechanism on transition probabilities.

### III. GENERALIZED DISTANCE BETWEEN ATTRACTORS

Accordingly to instructive conceptualization \[30\], each point in the genomic landscape (i.e. genome) provides epigenetic landscape of unique topology, which, due to its mathematical complexity, contains many stabilizing areas of space (attractors) around stable or equilibrium states. Transitions between attractors dominate in complex system’s behavior at its relevant time scales and represent additional force to the component of the force which follows gradient in the (quasi-potential) epigenetic landscape \[35\]. The system may contain countable set of attractors of different types adjoining each other and, intuitively, the probability of transitions between specific states depends on the depth and form of the respective attractors. Therefore, to put forward the above outlined conceptualization, the distributions (which are attractors in the functional space) must be specified. The arguments given here may be applied to simple, as well as highly complex parametrization.

Below we presume the attractors with normally distributed fluctuations. In such case we assume \( \theta_i \equiv (\mu_i, \sigma_i), i = 1, 2, \ldots, N, \) where \( \mu_i \) denotes the mean of the selected factor and \( \sigma_i \) its dispersion. Analogously, for the environment we assume the parametrization \( \theta^e(t) \equiv (\mu^e(t), \sigma^e(t)) \). Dissimilarity between the pairs of normal distributions is characterized by the Hellinger distance \[37\]. This original forms are modified by the regularization (see Appendix). In agreement with the assumptions and parametrization of the model discussed, we use regularized Hellinger distances in two contexts:

i) the inter-attractor form

\[
d^2_{ij} \equiv d^2(\mu_i, \sigma_i, \mu_j, \sigma_j, \epsilon) = 1 - \sqrt{\frac{2(\sigma_i + \epsilon)(\sigma_j + \epsilon)}{(\sigma_i + \epsilon)^2 + (\sigma_j + \epsilon)^2}} \times \exp \left(-\frac{1}{4} \frac{(\mu_i - \mu_j)^2}{(\sigma_i + \epsilon)^2 + (\sigma_j + \epsilon)^2} \right),
\]

and, ii) attractor-environment form

\[
d^2_i \equiv d^2(\mu_i, \sigma_i, \mu^e(t), \sigma^e(t), \epsilon) = 1 - \sqrt{\frac{2(\sigma_i + \epsilon)(\sigma^e(t) + \epsilon)}{(\sigma_i + \epsilon)^2 + (\sigma^e(t) + \epsilon)^2}} \times \exp \left(-\frac{1}{4} \frac{(\mu_i - \mu^e(t))^2}{(\sigma_i + \epsilon)^2 + (\sigma^e(t) + \epsilon)^2} \right).
\]

All the distances are regularized by the unique additive parameter \( \epsilon > 0 \), which plays the role of additional contribution to dispersion or determines respective generalized geometrical context. The functions are homogeneous of the order zero in the fol-
\[
d^2(\xi\mu_i, \xi\sigma_i, \xi\sigma_j, \xi\epsilon) = d^2(\mu_i, \sigma_i, \mu_j, \sigma_j, \epsilon), \\
d^2(\xi\mu_i, \xi\sigma_i, \xi\mu^c(t), \xi\sigma^c(t), \xi\epsilon) = \\
d^2(\mu_i, \sigma_i, \mu^c(t), \sigma^c(t), \epsilon). \\
(9)
\]

The above equation trivially induces scale invariance of the transition matrix. The independence on the scaling parameter \(\xi\) implies generality of the conclusions derived from the particular calculation, which makes relevant proportions of the parameters \(\mu_i\) and \(\sigma_i\), and time dependencies \(\mu^c(t)\) and \(\sigma^c(t)\) instead of their values themselves.

The idea of regularization is to keep dependence upon the \(\mu_i, \mu_j\) and \(\mu^c(t)\) even in the anomalous situation when the dispersions vanish

\[
d^2(\mu_i, 0, \mu_j, 0, \epsilon) = 1 - \exp\left(-\frac{(\mu_i - \mu_j)^2}{8\epsilon^2}\right), \\
d^2(\mu_i, 0, \mu^c(t), 0, \epsilon) = 1 - \exp\left(-\frac{(\mu_i - \mu^c(t))^2}{8\epsilon^2}\right).
\]

The above relationship indicates, that only \(\epsilon > 0\) guarantees sensitivity of the distance to the mean values also in the case of zero dispersions \(\sigma_i\) and \(\sigma_j\), now, instead of interest in particular attractor, we continue with the construction of the probabilistic model for the response probability density function \(P(x, t)\), representing the system of attractors, along some cumulative cell state characteristics \(x\), playing formally the role of interpolation variable. Note that \(x\) is assumed to have the same origin (i.e. the same meaning, dimension and unit) as \(\mu_i\) and \(\sigma_i\). Following above conceptualization, we express \(P(x, t)\) as a probabilistic multimodal Gaussian mixture model

\[
P(x, t) = \sum_{i=1}^{N} p_i(t) \phi_g(x; \mu_i, \sigma_i) \\
(11)
\]

based on the convex combination of \(N\) Gaussian response probability density functions

\[
\phi_g(x; \mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma}} \exp\left(-\frac{(x - \mu)^2}{2\sigma^2}\right). \\
(12)
\]

In this formula, the previously introduced probabilities \(\{ p_i(t) \}_{i=1}^{N}\) play the role of mixture weights. At the level of description using \(P(x, t)\), passing along the only parameter \(x\) comprises all the key observable statistical characteristics of the system of attractors, whereas \(\{ \mu_i, \sigma_i \}_{i=1}^{N}\) pairs may be viewed as partially hidden. The reader interested in consistency with the classical view of evolutionary biology may find it interesting, that instant fitness of the genetically identical cell population at given conditions \(x\) may be constructed as a monotonous function of

\[
\ln P(x, t) \text{ argument. The normalization}
\]

\[
\int_{-\infty}^{\infty} P(x, t)dx = \sum_{i=1}^{N} p_i(t) \int_{-\infty}^{\infty} dx \phi_g(x; \mu_i, \sigma_i) = 1
\]

stems from the obvious relations

\[
\int_{-\infty}^{\infty} \phi_g(x; \mu_i, \sigma_i) = 1, \quad \sum_{i=1}^{N} p_i(t) = 1. \\
(14)
\]

This model enables to determine the total mean, \(\mu(t)\), and the dispersion, \(\sigma(t)\), of \(P(x, t)\) as follows

\[
\mu(t) = \sum_{i=1}^{N} p_i(t) \mu_i, \\
\sigma^2(t) = \sum_{i=1}^{N} p_i(t) [ (\mu_i - \mu(t))^2 + \sigma_i^2 ]. \\
(16)
\]

The latter characteristics, \(\sigma(t)\), describes heterogeneity in attractors occupancies. Moreover, alternative and more adequate measures may be used for the same purposes. If specificity of attractors (comprised in \(\phi_g\)) is not taken into account one may use the classical Shannon’s definition

\[
S_{sh}(t) = -\sum_{i=1}^{N} p_i(t) \ln p_i(t). \\
(17)
\]

On the other hand, if one focuses on the stochastic transitions between attractors, then more appropriate measure is Markovian chain rates entropy

\[
S_{mr}(t) = -\sum_{i,j} p_i(t) W_{ij}(t) \ln W_{ij}(t). \\
(18)
\]

Because of nonlinear structure of the presented model, temporal behavior of both the entropy measures can only be provided by numerical integration. In the near future it would be also interesting to investigate Markovian framework of pheno-

\[
IV. \quad \text{NUMERICAL RESULTS}
\]

Below, illustrative numerical analysis of the system is performed for some particular numerical values of parameters. The calculation is performed for the system of \(N = 3\) states. For better understanding of numerical outputs, the states are characterized by the evenly distributed mean values: \(u_1 = 1, \mu_2 = 2, \mu_3 = 3\) and identical dispersions \(\sigma_1 = \sigma_2 = \sigma_3 = 0.3\). The parameters \(\beta = 1, \lambda = 0.1, \tau = 1\) have been
used to define $W_{ik}$. The time integration was performed by Euler method during which normalization condition $\sum_{i=1}^{N} p_i = 1$ was kept and integration step $\Delta t = 0.01$. We study only the stationary environmental statistics (see Fig. 1). We simulate system with the initial condition: $p_1(0) = 0.01$, $p_2(0) = 0.01$, $p_3(0) = 0.98$. The system is very distinct from preference represented by the properties of the environment $\mu^e = 1$, which supports much higher $p_1$. The expectation is confirmed by the solution of the master equation converging to $p_1(t) \gg p_1(0)$ (see Eq. 1).

![Figure 1](image1.png)

**FIG. 1:** The illustration of $N = 3$ state system and the non-equilibrium dynamic behavior of the probability density function $P(x,t)$. Part (a) The Gaussian peaks corresponding to the states $\mu_1 = 1, \mu_2 = 2, \mu_3 = 3$ and dispersions $\sigma_1 = \sigma_2 = \sigma_3 = 0.3$. The states are constructed using $\phi_g(x; \mu_i, \sigma_i)$. Part (b) The single peak corresponding to the environment with statistical properties $\mu^e = 1, \sigma^e = 0.4$. Constructed using $\phi_g(x; \mu^e, \sigma^e)$. Part (c) The difference in $P(x,t)$: the initial condition $P(x, 0)$ (constructed for initial weights $p_1(0) = 0.01$, $p_2(0) = 0.01$, $p_3(0) = 0.98$) from the asymptotic "three-hill" (caused by the differences in $\mu_i$) probability density function $P(x,t \rightarrow \infty)$.

![Figure 2](image2.png)

**FIG. 2:** The supplementary 3d view showing the variation of $P(x,t)$ until the limiting distribution is attained. Calculated for the same conditions as in Fig. 1. The formation of "tree-hill" (long-term) asymptotics is visible.

![Figure 3](image3.png)

**FIG. 3:** The non-equilibrium behavior of the Shannon entropy $S_{sh}$ (part a) and Markovian entropy rate $S_{mr}$ (part b). The complementary dependencies to those presented in Fig. 2 calculated for perturbations - 3 distinct environments with the same mean $\mu^e = 1$, but different dispersion $\sigma^e = 0.2, 0.6, 1.5$. The calculation shows the non-monotonously growing entropy (on the level of the clone) (see Eqs. 17, 18). The alternative information-theoretic measure, the Markovian entropy rate shows that transitions between attractors exhibit diversity decrease and saturation.
V. CONCLUSION

When therapeutic intervention is to consist exclusively in purposeful manipulation with the statistics of environment aimed to reduce non-genetic heterogeneity, the therapy may be formally viewed as the entropy minimization problem and solved by standard optimization techniques. To be more instructive, we propose the system of equations for \( \sigma^e(t) \) and \( \mu^e(t) \) that, in principle, represents steepest descent gradient dynamics which minimizes local term \((1/\tau_{sh} + d\ln S_{sh}/dt)^2\)

\[
\frac{d \ln \sigma^e}{dt} = -\gamma_S \left( \frac{1}{\tau_{sh}} + \frac{d \ln S_{sh}}{dt} \right) \left[ \frac{\partial}{\partial \ln \sigma^e} \left( \frac{d \ln S_{sh}}{dt} \right) \right] + \gamma_\sigma (\ln \sigma_0^e - \ln \sigma^e) \tag{19}
\]

\[
\frac{d \mu^e}{dt} = -\gamma_S \left( \frac{1}{\tau_{sh}} + \frac{d \ln S_{sh}}{dt} \right) \left[ \frac{\partial}{\partial \mu^e} \left( \frac{d \ln S_{sh}}{dt} \right) \right] + \gamma_\mu (\mu_0^e - \mu^e) \tag{20}
\]

where \( \tau_{sh} \) is required time of entropy decrease comparable to the time scale of switching dynamics (i.e. much smaller than evolutionary time scale), and \( \gamma_S \leq 0 \) controls the mechanism of entropy reduction. In Eq. (19), the term \( \ln \sigma^e \) is used instead of \( \sigma^e \) to keep the constraint \( \sigma^e \geq 0 \) for any eventual solution. The linear terms \( \propto \gamma_\mu, \propto \gamma_\sigma \) are used to bias eventual solutions towards long-term (i.e. viable) environment conditions \((\mu_0^e, \sigma_0^e)\). The above system of nonlinear equations (19, 20) must be solved simultaneously with equations for \( \{p_i(t)\}_{i=1}^N \) regarding actual form of \( S_{sh} \).

To sum up, to study cancer progression as evolutionary process, top-down causation must be respected. It implicitly challenges the question of predictability of evolutionary trajectory of cancer based exclusively on biochemical or genetic details. On the other hand, applying top-down causation enables to abstract from case-dependent implementation details and benefit from applying universal concepts developed in different branches of science. Here outlined conceptualization links uncertainty of instant environment quantified by the probability density function with the evolutionary tuned cell state probability density function. Presented conceptualization may help to apply inverse modeling approach, which means evolving desired phenotypic heterogeneity by purposeful manipulating environment uncertainty with the perspective of therapeutic impact.

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Appendix: Regularization of Hellinger distance for the pair of gaussian distributions

The purpose of this appendix is to review some elements of Hellinger distance calculus. We define the square of the Hellinger distance \( d^2 \) in terms of elementary probability theory. If we denote the parametrization of the probability densities as \( \phi(x, \theta) \), \( s = 1, 2 \), then the squared Hellinger distance can be expressed as

\[
d^2(\theta_1, \theta_2) = 1 - \int_{-\infty}^{\infty} \sqrt{\phi(x, \theta_1) \phi(x, \theta_2)} dx . \tag{21}
\]

In the case of the pair of two Gaussian distributions \( \phi_1(x, \mu_1, \sigma_1), \phi_2(x, \mu_2, \sigma_2) \) constructed from the ”template”

\[
\phi(x, \theta) \equiv \phi_b(x, \mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma}} \exp \left[ -\frac{(x - \mu)^2}{2\sigma^2} \right] \tag{22}
\]

we obtained

\[
d^2(\mu_1, \sigma_1, \mu_2, \sigma_2) = 1 - \frac{2\sigma_1\sigma_2}{\sigma_1^2 + \sigma_2^2} \exp \left( \frac{-(\mu_1 - \mu_2)^2}{4(\sigma_1^2 + \sigma_2^2)} \right) . \tag{23}
\]

Since the limit \((\sigma_1, \sigma_2) \to (0, 0)\) may create the interpretation problems, the original form of \( d^2(\cdot) \) should be regularized. One possible way is to use additive extra dispersion \( \epsilon > 0 \) as follows

\[
d^2(\mu_1, \sigma_1, \mu_2, \sigma_2, \epsilon) = 1 - \sqrt{\frac{2(\sigma_1 + \epsilon)(\sigma_2 + \epsilon)}{(\sigma_1 + \epsilon)^2 + (\sigma_2 + \epsilon)^2}} \times \exp \left( \frac{-((\mu_1 - \mu_2)^2}{4((\sigma_1 + \epsilon)^2 + (\sigma_2 + \epsilon)^2)} \right) . \tag{24}
\]

Thus, in the case when the original dispersions \( \sigma_1, \sigma_2 \) shrink to zero we have

\[
d^2(\mu_1, 0, \mu_2, 0, \epsilon) = 1 - \exp \left( \frac{-(\mu_1 - \mu_2)^2}{8\epsilon^2} \right) . \tag{25}
\]

Then the Taylor expansion of the previously obtained function at \( \mu_1 \sim \mu_2 \) yields

\[
d^2(\mu_1, 0, \mu_2, 0, \epsilon) = \frac{((\mu_1 - \mu_2)^2}{8\epsilon^2} - \frac{((\mu_1 - \mu_2)^4}{128\epsilon^4} + O((\mu_1 - \mu_2)^6) . \tag{26}
\]
with the leading term proportional to the dissimilarity measure analogous to the one dimensional quadratic Euclidean squared distance \((\mu_1 - \mu_2)^2\) between Cartesian coordinates \(\mu_1\) and \(\mu_2\) in 1d. Such demonstration of the asymptotic consistency be-
tween generalized distance measure of the probability distributions and classical analytical Euclidean distance in 1d supports the adequacy of \(\epsilon > 0\) regularization.

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