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VIABLE FLUX DISTRIBUTION IN METABOLIC NETWORKS

Ginestra Bianconi

The Abdus Salam ICTP, Strada Costiera 11, 34014 Trieste, Italy

Riccardo Zecchina

Politecnico di Torino,Corso Duca degli Abruzzi, 34,I-10129, Torino, Italy

Abstract. The metabolic networks are very well characterized for bacterial such of *E.coli*. For this reason they provide a 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 [1, 9, 24, 25] on the dynamics defined on them [10]. Important examples of the dynamics on networks with relevant applications are the Ising model [11, 19, 3], the spreading of a disease [26] and the synchronization models [23, 22]. In this paper we 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 [18] 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 [33] for a large number of organisms in the three different domains of life (archea, 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 [17, 27, 31]. 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 [13, 14, 16] 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

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of the reactions in the graph for a given environment and it constitute a real breakthrough 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 [28, 30]. The problem of identifying the flux distribution in *Escherichia coli* was studied experimentally [12] and by means of Flux-Balance-Analysis [2] . A fat tail in their distribution with different power-law exponents $\alpha < 2$ was found.

Metabolic networks provide a very interesting framework for the construction 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 distribution as the real ones i.e. networks in the the hidden-variable ensemble [7, 6, 15] with same expected degree distribution as the metabolic factor graphs. Formally the problem is resolved with replica calculations on diluted networks [19] extended to the case of continuous variables. Due the simplicity of the Hamiltonian the problem is solved with an expansion of the order parameter in terms of Gaussians. The problem shares some similarity with other problems in statistical mechanics of disordered systems [4, 29]. In two recent papers [8, 5] a similar approach has been pursued. In [8] the metabolic network 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. In [5] a very similar approach to the one we are going to present was studied numerically.

2. **The model.** The metabolic network has a bow tie structure [31], therefore the metabolites can be 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 stoichiometric matrix is given by $((\xi_{\mu,i}))$ where $\mu = 1, \dots, M$ indicates the metabolite and $i = 1, \dots, N$ the reaction and the sign of $\xi_{\mu,i}$ indicates if the metabolite μ 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_μ which is consumed/produced by a reaction i at a rate s_i which indicates the flux of each reaction i in the metabolic network. We assume that the metabolites μ are produced or consumed at a fixed rate, i.e.

$$\frac{dc_\mu}{dt} = \sum_i \xi_{\mu,i} s_i = g^\mu \tag{1}$$

In particular for intermediate metabolites we assume steady state and $g_\mu = 0$. Instead for input/output metabolites we assume $g_\mu < 0$, $g_\mu > 0$ respectively, fixing in this way the rates or consumption of metabolites from the environment and of production of biomass.

To mimic biological constraints on the concentrations of the enzymes we consider only fluxes in within an ellipse of semi-axis $\sqrt{q_i}\Lambda_i$ i.e.

$$\frac{1}{\langle q \rangle N} \sum_i q_i \left(\frac{s_i}{\Lambda_i} \right)^2 = L'. \tag{2}$$

and $L' \leq L$. In other words the parameter Λ_i is fixes the typical flux of reaction i and the global sherical contraint Eq.(2) limit the average flux to be lower that L. For simplicity in the following we will take $\Lambda_i = 1$ $\forall i = 1, \dots, N$. The volume of

solutions V, given the constraints (1) and (2), is proportional to the quantity

$$\tilde{V} = \int_0^L dL' \int \prod_{i=1}^{N} ds_i \prod_{\mu} \delta(\sum_i \xi_{\mu,i} s_i - g^{\mu}) \delta(\sum_j q_j (s_j/\Lambda_j)^2 - N\langle q \rangle L'^2). \tag{3}$$

To consider analytical tractability of the problem we assume that the all the reactions are potentially reversible. Consequently we assume that the fluxes have no definite sign. In Ref. [5] the problem is solved by numerical integration of the belief propagation (BP) equations derived by the estremization of the volume of solution (3) respect to the flux distribution.

3. **Replica method.** We assume that the support of our stochiometric matrix is a random uncorrelated network with given degree distribution, i.e. a realization of the random hidden-variable model [7, 6, 15]. In particular we fix the expected degree distribution of the nodes of the factor graphs to be q_i for the reaction node $i = 1, \dots N$ and q_μ for the metabolite nodes $\mu = 1, \dots, M$ and we assume that the matrix elements $\xi_{\mu,i}$ are distributed following

$$P(\xi_{\mu,i}) = \frac{q_i q_\mu}{2\langle q_i \rangle N} [\delta(\xi_{\mu,i} - 1) + \delta(\xi_{\mu,i} + 1)] + \left(1 - \frac{q_i q_\mu}{\langle q_i \rangle N}\right) \delta(\xi_{\mu,i}), \tag{4}$$

where $\delta()$ indicates the Kronecker delta. Note that in (4) we have assumed that the elements of the stochiometric matrix have values $0, \pm 1$ with a random sign and that the variables q_i q_μ are nothing else than the hidden-variables associated with metabolite μ of the reaction i of the hidden-variable network ensemble [7, 6, 15].

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 $S = \langle \log(Z) \rangle = \lim_{n \to 0} \frac{\langle \tilde{V}^n \rangle - 1}{n}$. The averaged volume of solutions $< \tilde{V}^n >$ can be expressed in the large N limit as

$$< \tilde{V}^n > = \int_0^L dL' \int \prod_a d\omega^a \int \prod_{a,i} ds_{i,a} \int \prod_{a,\mu} d\lambda_{\mu,a} \exp\left[-ig_\mu \sum_a \lambda_{\mu,a}\right]$$
$$\exp\left[-\sum_{i,\mu} \frac{q_i q_\mu}{\langle q_i \rangle N} (1 - \cos \vec{\lambda}_\mu \cdot \vec{s}_i) + i \sum_a \omega^a \left(\sum_j q_j s_{j,a}^2 - L'^2 \langle q_i \rangle N\right)\right], \tag{5}$$

where for simplicity we have choose $\Lambda_i = 1$ $\forall i$. Using the techniques coming from the field of diluted systems, we introduce the order parameters [21, 19]

$$c(\vec{\lambda}) = \frac{1}{\langle q_i \rangle N} \sum_\mu q^\mu \prod_a \delta(\lambda_{\mu,a} - \lambda_a)$$
$$c(\vec{s}) = \frac{1}{\langle q_i \rangle N} \sum_i q^i \prod_a \delta(s_{i,a} - s_a). \tag{6}$$

The order papameter $c(s)$ is a weighted flux distribution, and in the following we will refer to it as the flux distribution.

getting for the volume

$$\left\langle \tilde{V}^n \right\rangle = \int \mathcal{D}c(\vec{\lambda}) \int \mathcal{D}\hat{c}(\vec{\lambda}) \int \mathcal{D}c(\vec{s}) \int \mathcal{D}\hat{c}(\vec{s}) \exp[nN\langle q_i \rangle \Sigma(\hat{c}(\vec{\lambda}), c(\vec{\lambda}), \hat{c}(\vec{s}), c(\vec{s}))]$$

with

$$
\begin{aligned}
n\Sigma &= \int d\vec{\lambda} i\hat{c}(\vec{\lambda})c(\vec{\lambda}) + \int d\vec{s} i\hat{c}(\vec{s})c(\vec{s}) - \int d\vec{\lambda}\int d\vec{s} c(\vec{\lambda})c(\vec{s})(1-\cos(\vec{\lambda}\cdot\vec{s})) + \\
&+ \frac{1}{\langle q_i\rangle N}\sum_{\mu}\log\int d\vec{\lambda}\exp[-ig_\mu\sum_a\lambda_a - iq_\mu\hat{c}(\vec{\lambda})] - i\sum_a\omega_a L'^2 \\
&+ \frac{1}{\langle q_i\rangle N}\sum_{i}\log\int d\vec{s}\exp[-iq_i\hat{c}(\vec{s}) + i\sum_a q_i\omega_a s_a^2].
\end{aligned}
$$

The saddle point equations for evaluating Σ are given by

$$
\begin{aligned}
i\hat{c}(\vec{\lambda}) &= \int d\vec{s} c(\vec{s})(1-\cos(\vec{\lambda}\cdot\vec{s})) \\
i\hat{c}(\vec{s}) &= \int d\vec{\lambda} c(\vec{\lambda})(1-\cos(\vec{\lambda}\cdot\vec{s})) \\
c(\vec{\lambda}) &= \frac{1}{\langle q_i\rangle N}\sum_\mu q_\mu \frac{\exp\left[-ig_\mu\sum_a\lambda_a - iq_\mu\hat{c}(\vec{\lambda})\right]}{\int\prod_a d\lambda'_a\exp\left[-ig_\mu\sum_a\lambda'_a - iq_\mu\hat{c}(\vec{\lambda}')\right]} \\
c(\vec{s}) &= \frac{1}{\langle q_i\rangle N}\sum_i q_i \frac{\exp\left[-iq_i\hat{c}(\vec{s}) + i\sum_a\omega_a s_a^2\right]}{\int d\vec{s}'\exp\left[-iq_i\hat{c}(\vec{s}') + i\sum_a\omega_a(s')_a^2\right]} \\
L^2 &= \frac{1}{\langle q_i\rangle N}\sum_i q_i \frac{\int d\vec{s} s_a^2\exp[-iq_i\hat{c}(\vec{s}) + i\sum_a q_i\omega^a s_a^2]}{\int d\vec{s}'\exp[-iq_i\hat{c}(\vec{s}) + i\sum_a q_i\omega_a s_a^2]}.
\end{aligned}
\tag{7}
$$

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 $\vec{x}$ are identically equal distributed,

$$
c(\vec{z}) = \int d\vec{x} P(\vec{x})\prod_{a=1}^{n}\phi(z_a|\vec{x}) \tag{8}
$$

where $\phi(z|\vec{x})$ are distribution functions of z and $P(\vec{x})$ is a probability distribution of the vector field $\vec{x}$. For the function $\phi(z|\vec{x})$ the exponential form is usually assumed in Ising models. In our continuous variable case for our quadratic problem, we assume instead that $\phi(z|\vec{x})$ has a Gaussian form. This assumption could be in general considered as an approximate solution of the equations (7). Explicitly we assume that the functions $c(\vec{\lambda})$ and $c(\vec{s})$ can be expressed as the following,

$$
\begin{aligned}
c(\vec{\lambda}) &= \int dm_\lambda dh_\lambda P(h_\lambda, m_\lambda)\prod_a\exp\left[-\frac{1}{2}h_\lambda\lambda_a^2 + \frac{1}{2}\frac{m_\lambda^2}{h_\lambda}\right]\cos[m_\lambda\lambda_a]\sqrt{\frac{h_\lambda}{2\pi}} \\
c(\vec{s}) &= \int dm_s dh_s P(h_s, m_s)\prod_a\exp\left[-\frac{1}{2}h_s s_a^2 - \frac{1}{2}\frac{m_s^2}{h_s}\right]\cosh[m_s s_a]\sqrt{\frac{h_s}{2\pi}} \\
\omega_a &= i\omega
\end{aligned}
\tag{9}
$$

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

$$
\begin{aligned}
\hat{c}(\vec{s}) &= -i\left(1 - \int dm_\lambda dh_\lambda P(h_\lambda, m_\lambda)\prod_a\exp\left[-\frac{1}{2h_\lambda}s_a^2\right]\cosh[m_\lambda s_a/h_\lambda]\right) \\
\hat{c}(\vec{\lambda}) &= -i\left(1 - \int dm_s dh_s P(h_s, m_s)\prod_a\exp\left[-\frac{1}{2h_s}\lambda_a^2\right]\cos[m_s\lambda_a/h_s]\right).
\end{aligned}
\tag{10}
$$

The saddle point equations (7), taking into account the expression for the order parameters (9)(10) closes and can be written as recursive equation for $P(h_\lambda, m_\lambda)$ and $P(h_s, m_s)$, i.e.

$$
\begin{aligned}
P(h_\lambda, m_\lambda) &= \frac{1}{\langle q_i \rangle N} \sum_\mu q_\mu \sum_k e^{-q_\mu} q_\mu^k \frac{1}{k!} \int_{\dots} \int \prod_{l=1}^{k} dh_s^l dm_s^l \prod_l P(h_s^l, m_s^l) \\
&\quad \delta\left(h_\lambda - \sum_{l=1}^{k} \frac{1}{h_s^l} \right) \frac{1}{2^k} \sum_{\{n_l\}} \delta\left(m_\lambda - \sum_i (-1)^{n_l} \frac{m_s^l}{h_s^l} - g_\mu \right) \\
P(h_s, m_s) &= \frac{1}{\langle q_i \rangle N} \sum_i q_i e^{-q_i} \sum_k q_i^k \frac{1}{k!} \int_{\dots} \int \prod_{l=1}^{k} dh_\lambda^l dm_\lambda^l \prod_i P(h_\lambda^l, m_\lambda^l) \\
&\quad \delta\left(h_s - \sum_{i=1}^{k} \frac{1}{h_\lambda^l} - 2\omega q_i \right) \frac{1}{2^k} \sum_{\{n_l\}} \delta\left(m_s - \sum_i (-1)^{n_l} \frac{m_\lambda^i}{h_\lambda^l} \right) \qquad (11) \\
L^2 &= \frac{1}{\langle q^i \rangle N} \sum_i q^i e^{-q^i} \sum_k \frac{q_i^k}{k!} \sum_{s_i} \frac{1}{2^k} \int_{\dots} \int \prod_{l=1^k} dh_\lambda^l dm_\lambda^l \prod_l P(h_\lambda^l, m_\lambda^l) \\
&\quad \delta\left(H - \sum_{l=1}^{k} \frac{1}{h_\lambda^l} - 2\omega q_i \right) \frac{1}{2^k} \sum_{\{n_l\}} \delta\left(M - \sum_i (-1)^{n_l} \frac{m_\lambda^l}{h_\lambda^l} \right) (H + M^2).
\end{aligned}
$$

In these last expressions we indicated by n_l some auxiliary variables that can take values 0 or 1.

Finally S can be calculated at the saddle point as

$$
\begin{aligned}
S &= -\int dh_s dm_s dh_\lambda dm_\lambda P(h_s, m_s) P(h_\lambda, m_\lambda) \left[-\frac{(m_s/h_s)^2}{2(h_\lambda + 1/h_s)} + \frac{(m_\lambda/h_\lambda)^2}{h_s + 1/h_\lambda} + \right. \\
&\quad \left. + \ln \cosh\left(\frac{m_s m_\lambda}{h_s h_\lambda + 1} \right) + \frac{1}{2} \ln \frac{1}{h_\lambda h_s + 1} \right] + \qquad (12) \\
&\quad + \frac{1}{\langle q^i \rangle N} \sum_\mu \sum_k e^{-q_\mu} q_\mu^k \frac{1}{k!} \int \prod_{l=1}^{k} dh_s^l dm_s^l P(h_s^l, m_s^l) \\
&\quad \left\{ \frac{1}{2^{k+1}} \left[\frac{g_\mu^2 + \sum_j (m_{s,j}/h_{s,j})^2}{\sum_j \frac{1}{h_s^j}} \right] - \frac{1}{2} \ln \sum_j \frac{1}{h_s^j} \right\} \\
&\quad - \frac{1}{\langle q_i \rangle N} \sum_i \sum_k e^{-q_i} \, q_i^k \frac{1}{k!} \int \prod_l dh_\lambda^l dm_\lambda^l P(h_\lambda^l, m_\lambda^l) \\
&\quad \left\{ \frac{1}{2^k} \left[\frac{\sum_j (m_{\lambda,j}/h_{\lambda,j})^2}{\sum_j \frac{1}{h_{\lambda,j}} + 2\omega q_i} \right] - \frac{1}{2} \ln \left[\sum_j h_\lambda^j + 2\omega q_i \right] \right\}
\end{aligned}
$$

4. **Population dynamics.** We solved the equations (11) by a population-dynamical algorithm. We represent the effective field distributions (h_s, m_s) (h_λ, m_λ) by a large population of $P \gg 1$ fields. Running the algorithm the population is first initialized randomly and then equations (11) are used to iteratively replace the fields inside the population until convergence is reached. We fix

the value of the lagrangian multiplier ω to account for a fixed average value of L^2. The action of the algorithm is summarized in the following pseudo code

algorithm PopDyn($\{h_s^1, m_s^1, h_s^2, m_s^2, \dots, h_s^P, m_s^P\}$; $\{h_\lambda^1, m_\lambda^1, h_\lambda^2, m_\lambda^2, \dots, h_\lambda^P, m_\lambda^P\}, \omega$)
begin do

- choose a reaction i_0 with probability $q_i P(q_i)$;
- draw d from a Poisson distribution $(e^{-q_i} q_i^k/k!)$
- select d indexes $i_1, \dots i_d \in \{1, \dots M\}$
- draw a d-dimensional vector $\vec{n} = \{n_i\}$ of random numbers $n_i = 0, 1$

$$\begin{aligned} h_s^{i_0} : &= \sum_{l=1}^{d} \frac{1}{h_\lambda^{i_l}} + 2\omega q_i; \\ m_s^{i_0} : &= \sum_{l=1}^{d} (-1)^{n_l} \frac{m_\lambda^{i_l}}{h_\lambda^{i_l}}; \\ L_2 : &= \left(1 - \frac{1}{\langle q^i \rangle N}\right) L_2 + \frac{1}{\langle q_i \rangle N} \frac{h_s^{i_0} + (m_s^{i_0})^2}{(h_s^{i0})^2}; \end{aligned} \tag{13}$$

- choose a random metabolite μ_0 with probability $q_\mu P(q_\mu)$
- draw d from a Poisson distribution $(e^{-q_\mu} q_\mu^k/k!)$
- select d indexes $i_1, \dots i_d \in \{1, \dots M\}$
- draw a d-dimensional vector $\vec{n} = \{n_i\}$ of random numbers $n_i = 0, 1$

$$\begin{aligned} h_\lambda^{\mu_0} : &= \sum_{l=1}^{d} \frac{1}{h_s^{i_l}}; \\ m_\lambda^{\mu_0} : &= \sum_{l=1}^{d} (-1)^{n_l} \frac{m_s^{i_l}}{h_s^{i_l}} + g^{\mu_0} \end{aligned} \tag{14}$$

while (not converged) **return end**

We run the population dynamics algorithm and we measure the distribution of fluxes $P(s)$ for different values of ω. We consider as the underline network a network with the real degree distribution of the metabolic factor graph of Escherichia coli and on a network with the same number of metabolites and reactions as the real Escherichia coli 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). The flux distributions $c(s)$ depend significantly on the input/output flux. In Fig. 1 we report the results in the case $g^\mu = 0$ for all metabolites. In particular we show the flux distribution $c(s)$ for different value of ω: *i)* for the random network with the same degre distribution as the metabolic network of E. coli and *ii)* for the random network with two delta function degree distribution ($P(q_i) = \langle q_i \rangle$, $P(q_\mu) = \langle q_i \rangle N/M$). We observe that flux distribution for the random graph with the same degree distribution as E.coli allow for larger fluctuations of the fluxes. In Fig 2 we report the results in the case in which the incoming and outgoing fluxes are applied to 15% of the metabolites to be $g^\mu = g_0$. The random graphs with the same degree distribution of the real metabolic networks of E.coli develops a power-law tail with an exponent α depending on g_0.

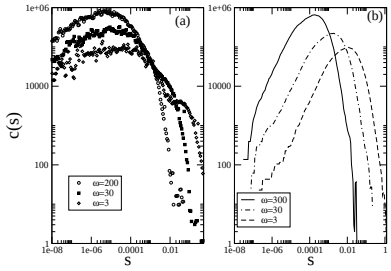

FIGURE 1. Flux distribution $c(s)$ with different values of ω. Inset (a) show the results for a random network with the same degree distribution of the metabolic network of Escherichia coli. Inset (b) show the results for a random graph with the same number of metabolites and reactions and the same number of nodes that the real metabolic network of Escherichia coli but with two delta peaks for the degree distribution.

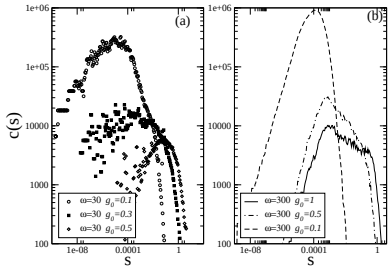

FIGURE 2. Flux distribution $c(s)$ with different values of the input flux g_0. Inset (a) show the results for a random network with the same degree distribution of the metabolic network of Escherichia coli. Inset (b) show the results for a random graph with the same number of metabolites and reactions and the same number of nodes that the real metabolic network of Escherichia coli but with two delta peaks for the degree distribution.

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. This method when considering the real degree distributionof E.coli generates flux distribution with the higher variance respect to graph with more uniform distribution. 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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E-mail address: gbiancon@ictp.it
E-mail address: riccardo.zecchina@polito.it