Présentation réalisée avec le soutien
du projet ERC COMBINEPIC

Large fluctuations in multi-scale modeling for rest hematopoiesis

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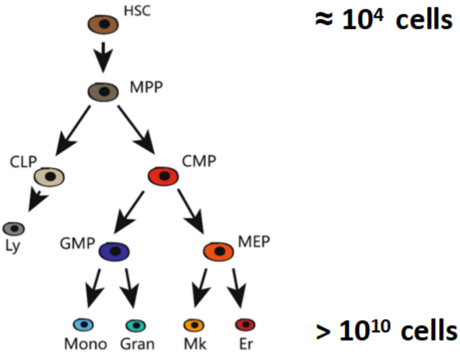
erc

Une marche aléatoire inspirée d'une dynamique cellulaire



Decomposable structure : no loop in differentiation

Multi-scale parameters

- $N(t) = (N_1(t), N_2(t), N_3(t))$: Cell of each type number at time t.

First type assumption

$$N_1(t=0) \sim K >> 1$$

Multi-scale assumptions

$$p_2^D - p_2^R = K^{-\gamma_2} \quad \text{and} \quad \tau_3 = c_3 K^{-\gamma_3}$$

with

$$(\gamma_2, \gamma_3) \in]0,1[\quad \text{and} \quad c_3 > 0.$$

In this presentation

$$\gamma_2 < \gamma_3 < 1.$$

Simulations

We take as initial condition

$$N^K(0) = (K, 0, 0)$$

Then values used are

$$K = 2000, \quad \gamma_2 = 0.55, \quad \gamma_3 = 0.8.$$

All the others parameters are equal to 1.

$K^{\gamma_2} \sim 60$ and $K^{\gamma_3} \sim 400$

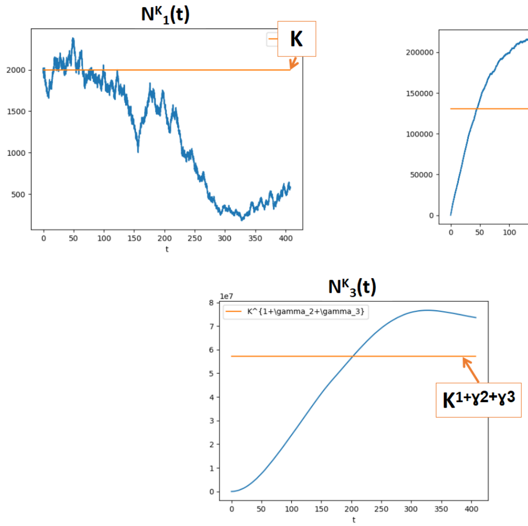


FIGURE – A trajectory of the N^K process for $t \in [0, T]$ with $T = 400$

$K^{\gamma_2} \sim 60$ and $K^{\gamma_3} \sim 400$

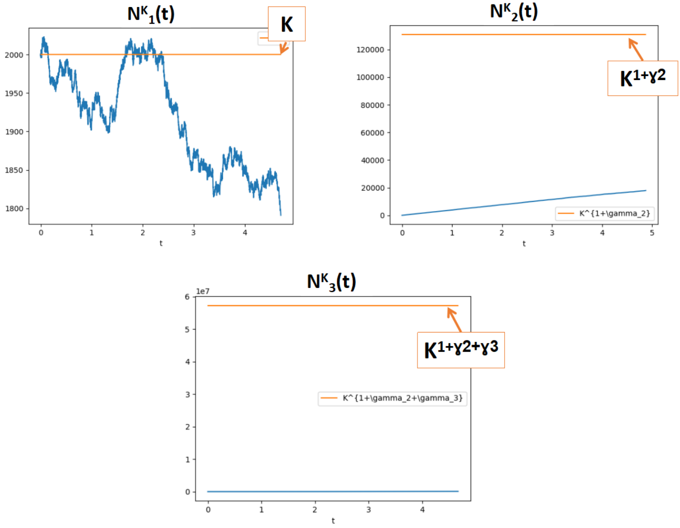


FIGURE – A trajectory of the N^K process for $t \in [0, T]$ with $T = 5$

Focus on the slow component ($\gamma_2 < \gamma_3$)

For all $t \geq 0$,

$$Z^K(t) = \left(\frac{N_1^K(t\,K^{\gamma_3})}{K}, \frac{N_2^K(t\,K^{\gamma_3})}{K^{1+\gamma_2}}, \frac{N_3^K(t\,K^{\gamma_3})}{K^{1+\gamma_2+\gamma_3}}\right).$$

$\forall t \geq 0$,

$$Z_1^K(t) = Z_1^K(0) + R_1^K(t)$$

$$Z_2^K(t) = Z_2^K(0) + K^{\gamma_3-\gamma_2}\left(\int_0^t \tau_1\, Z_1^K(s)\, ds - \int_0^t \tau_2\, Z_2^K(s)\, ds\right) + R_2^K(t)$$

$$Z_3^K(t) = Z_3^K(0) + \int_0^t 2\, p_2^D \tau_2\, Z_2^K(s)\, ds - \int_0^t c_3\, Z_3^K(s)\, ds + R_3^K(t)$$

Focus on the slow component ($\gamma_2 < \gamma_3$)

For all $t \geq 0$,

$$Z^K(t) = \left(\frac{N_1^K(t\,K^{\gamma_3})}{K}, \frac{N_2^K(t\,K^{\gamma_3})}{K^{1+\gamma_2}}, \frac{N_3^K(t\,K^{\gamma_3})}{K^{1+\gamma_2+\gamma_3}}\right).$$

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$$Z_3^K(t) = Z_3^K(0) + \int_0^t 2\, p_2^D \tau_2\, Z_2^K(s)\, ds - \int_0^t c_3\, Z_3^K(s)\, ds + R_3^K(t)$$

Habituellement

- Tension de la suite de loi de Z^K

$$\forall \epsilon, \exists C > 0, \quad \mathbb{P}\big(\sup_{t \in [0,T]} \| Z^K(t) \| > C\big) < \epsilon$$

- Théorème de Prohorov

Convergence to the deterministic model

Let Γ_2^K be the occupation measure of Z_2^K given by

$$\Gamma_2^K([0,t] \times B) = \int_0^t \mathbf{1}_B(Z_2^K(s))ds.$$

Under some assumptions on initial condition

Theorem

Assume

$$Z_1^K(0) \xrightarrow[K\to\infty]{\mathcal{L}} z_0^{(1)}.$$

Then

$$\Gamma_2^K \xrightarrow[K\to\infty]{} \delta_{z_2^*}(dz_2)\, ds \quad \text{with} \;\; z_2^* = \frac{\tau_1 z_0^{(1)}}{\tau_2}.$$

Convergence to the deterministic model

Under some assumptions on initial condition,

Theorem

Assume

$$(Z_1^K(0), Z_3^K(0)) \xrightarrow[K\to\infty]{\mathcal{L}} (z_0^{(1)}, z_0^{(3)}).$$

Then for all $T > 0$*,*

$$((Z_1^K, Z_3^K), \quad t \in [0,T])_K \xrightarrow[K\to\infty]{\mathbb{P}} ((z_1, z_3), \quad t \in [0,T]).$$

The functions z_1 *and* z_3 *are given by,* $\forall t \geq 0$*,*

$$\begin{cases} z_1(t) &= z_0^{(1)} \\ z_3(t) &= \frac{\tau_2}{c_3} z_2^* + \left(z_0^{(3)} - \frac{\tau_2}{c_3} z_2^*\right) e^{-c_3 t} \end{cases} \quad \textit{with} \quad z_2^* = \frac{\tau_1 z_0^{(1)}}{\tau_2}.$$

Large fluctuations

Let define

$$\forall t \geq 0, \quad \begin{cases} V_1^K(t) & = K^{(1-\gamma_3)/2}\big(Z_1^K(t) - z_0^{(1)}\big) \\ V_2^K(t) & = \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}}\big(Z_2^K(t) - Z_2^K(0)\big) \\ V_3^K(t) & = K^{(1-\gamma_3)/2}\big(Z_3^K(t) - z_3(t)\big) \end{cases} .$$

Large fluctuations (rappel : $\gamma_2 < \gamma_3 < 1$)

$\forall t \geq 0$,

$$\mathbb{E}\left[R_1^K(t)^2\right] = K^{-(1-\gamma_3)} \int_0^t 2\tau_1 \, \mathbb{E}\left[Z_1^K(s)\right] ds$$

$$\mathbb{E}\left[R_2^K(t)^2\right] = K^{-(1+2\gamma_2-\gamma_3)} \int_0^t \tau_1 \, \mathbb{E}\left[Z_1^K(s)\right] ds + K^{-(1+\gamma_2-\gamma_3)} \int_0^t \tau_2 \, \mathbb{E}\left[Z_2^K(s)\right] ds$$

$$\mathbb{E}\left[R_3^K(t)^2\right] = K^{-(1+\gamma_2+\gamma_3)} \int_0^t \left(4\, p_2^D \tau_2 \, \mathbb{E}\left[Z_2^K(s)\right] + c_3 \mathbb{E}\left[Z_3^K(s)\right]\right) ds.$$

Why $V_2^K = \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}}\big(Z_2^K(t) - Z_2^K(0)\big)$?

$$\big(Z_3^K(t) - z_3(t)\big) = \big(Z_3^K(0) - z_3(0)\big) - \tau_3 \int_0^t \big(Z_3^K(s) - z_3(s)\big)ds + (1 + \frac{1}{K^{\gamma_2}})\tau_2 \int_0^t \big(Z_2^K(s) - z_2^*\big)ds + R_3^K(t)$$

where

$$\tau_2 \int_0^t \big(Z_2^K(s) - z_2^*\big)ds = \tau_1 \int_0^t \big(Z_1^K(s) - x_1\big)ds - \frac{Z_2^K(t) - Z_2^K(0)}{K^{\gamma_3-\gamma_2}} + \frac{R_2^K(t)}{K^{\gamma_3-\gamma_2}}.$$

Why $V_2^K = \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}}(Z_2^K(t) - Z_2^K(0))$?

Under some assumptions on initial condition,

Theorem

Assume

$$\lim_{K\to\infty} \mathbb{E}\big[V_2^K(0)^2\big] = 0$$

then

$$\forall T \geq 0, \quad \lim_{K\to\infty} \mathbb{E}\big[\sup_{t\in[0,T]} V_2^K(t)^2\big] = 0.$$

$$\forall t \geq 0, \quad V_3^K(t) = V_3^K(0) + 2\,p_2^D \int_0^t \tau_1\, V_1^K(s)\,ds - c_3 \int_0^t V_3^K(s)\,ds$$
$$+ K^{(1-\gamma_3)/2} R_3^K(t) + 2\,p_2^D \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}} R_2^K(t) - 2\,p_2^D\, V_2^K(t).$$

Why $V_2^K = \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}}\left(Z_2^K(t) - Z_2^K(0)\right)$?

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$$+ K^{(1-\gamma_3)/2} R_3^K(t) + 2\, p_2^D \frac{K^{(1-\gamma_3)/2}}{K^{\gamma_3-\gamma_2}} R_2^K(t) - 2\, p_2^D\, V_2^K(t).$$

Large fluctuations

Under some assumptions on initial condition,

Theorem

Assume

$$(V_1^K(0), V_3^K(0)) \xrightarrow[K\to\infty]{\mathcal{L}} (V_0^{(1)}, V_0^{(3)}).$$

Then for all $T > 0$*,*

$$((V_1^K(t), V_3^K(t)), \quad t \in [0, T])_K \xrightarrow[K\to\infty]{\mathcal{L}} ((V_1(t), V_3(t)), \quad t \in [0, T])$$

such that

$$\forall t, \quad V_1(t) = V_0^{(1)} + \sqrt{\tau_1 \, z_0^{(1)}} B_1(t)$$

$$V_3(t) = V_0^{(3)} + \tau_1 \int_0^t V_1(s) ds - c_3 \int_0^t V_3(s) \, ds,$$

where B_1 *is a standard Brownian motion.*

Interpretation

Assume
$$Z_3^K(0) = z_3^*.$$
When K is large,
$$N_3^K(t\,K^{\gamma_3}) \sim z_3^*\,K^{1+\gamma_2+\gamma_3} + V_3(t)\;\underbrace{\frac{K^{1+\gamma_2+\gamma_3}}{K^{(1-\gamma_3)/2}}}_{>K^{(1+\gamma_2+\gamma_3)/2}}$$
with
$$\forall t,\quad V_3(t) = \tau_1 \int_0^t V_1(s)ds - c_3 \int_0^t V_3(s)\,ds,$$
$$\forall t,\quad V_1(t) = \sqrt{\tau_1\,z_0^{(1)}}\,B_1(t)$$

Thank you for your attention ! !

My collaborators

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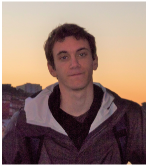

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