Supporting Information

for the article ***Modeling cell populations metabolism and competition under maximum power constraints*** by Conte L. et al.

A. Parameter estimation

We consider the bone marrow (BM) as the tissue where normal and malignant PCs grow - playing the role of the micro-environment. We estimate the carrying capacity K as the total number of cells that can proliferate in the bone marrow in ATP equivalent units so that $K \sim 4.05 \cdot 10^{21}$ *ATPeq* with

$K \cong$ (n. of cells in human body)·(% bone marrow volume in body)·(ATP in a cell) (S1)

where the total number of cells in the human body is $3 \cdot 10^{12}$ cells [1; 2], the volume occupied by the bone marrow (1.75 L) [1] within a standard weight human body (65 L) [1] is ~2.7% of the total body volume, and the ATP required to build up a cell is $5 \cdot 10^{10}$ ATP molecules per cell [1; 2].

We estimate the steady-state value of the stock of the adapted population (normal PCs), Q_{ss}, as the average fraction of plasma-cells typically found in the BM, so that $Q_{ss} \sim 8.1 \cdot 10^{19}$ *ATPeq* $\cong 0.02 \cdot K$, where the average fraction of plasma cells in the bone marrow is ~2% [3].

The phenomenological efficiency η is estimated for both normal and neoplastic plasma cells ($\eta_1 = \eta_2$) as the efficiency of mitochondrial respiration $\eta \sim 40\%$ [4].

We estimate the parameter τ from measures of cell proteome turnover time, defined as the time for a cell to completely regenerate its proteome with newly synthesized proteins. From quantitative proteomics studies - performed with stable isotope labeling by amino acids in cell culture (SILAC) techniques [5; 6; 7; 8] we estimate $\tau \sim 72\ h$ both for normal and neoplastic PCs.

We estimate the parameter r for malignant PCs (r_m) from observations of proliferation rates of neoplastic plasma cell populations combined with the estimate for $\tau \sim 72\ h$. The proliferation rate, or relative growth rate (*RGR*), is typically measured with the Ki-67 flow cytometry technique performed on clinical samples for patients affected by multiple-myeloma disease at different developmental stages [9; 10; 11; 12]. We estimate r_m from the approximation of Eq.5 for small times, resampling in-vitro experimental conditions. For small times, Eq.5 has an exponential solution for Q that only depends on the relative growth rate $RGR = r - 1/\tau$

$$\frac{dQ}{dt} \simeq RGR \cdot Q = \left(r - \frac{1}{\tau}\right) \cdot Q \qquad \text{(S2)}$$

thus $r = RGR + 1/\tau$. We us1 reported typical values for *RGR* (3%-10%) and τ (72 *h*) to estimate $r_m \sim 1.43 \cdot 10^{-2}$ - $1.53 \cdot 10^{-2}\ h^{-1}$ for different malignant PCs phenotypes.

We infer the parameter r for normal PCs (r_n) inverting the analytical expression for $Q_{ss} = K \cdot (1 - 1/r \cdot \tau)$, from estimates of $Q_{ss} \sim 8.1 \cdot 10^{19}$ *ATPeq*, $K \sim 4.05 \cdot 10^{21}$ *ATPeq* and $\tau \sim 72\ h$. Thus $r_n \sim 1.39 \cdot 10^{-2}\ h^{-1}$ for normal PCs.

B. Analytical sensitivity analysis

We derive the analytical sensitivities of the quantities Q and P in steady state, Q_{ss} and P_{ss}, for the single population model in Eq. 7. The expression for $Q_{ss}=K\cdot(1-1/r\cdot\tau)$ and $P_{ss}=(K/\tau)\cdot(1-1/r\cdot\tau)$ both depend on K, r and τ . Their sensitivity with respect to change in these parameters is calculated as differentials of thermodynamic observables

$$dP_{ss} = \left(\frac{\partial P_{ss}}{\partial K}\right)_{r,\tau} dK + \left(\frac{\partial P_{ss}}{\partial r}\right)_{K,\tau} dr + \left(\frac{\partial P_{ss}}{\partial \tau}\right)_{K,r} d\tau \qquad \text{(S3)}$$

$$dQ_{ss} = \left(\frac{\partial Q_{ss}}{\partial K}\right)_{r,\tau} dK + \left(\frac{\partial Q_{ss}}{\partial r}\right)_{K,\tau} dr + \left(\frac{\partial Q_{ss}}{\partial \tau}\right)_{K,r} d\tau \qquad \text{(S4)}$$

In our case study, we fix τ and K and change r for different phenotypes of neoplastic plasma cells, exploiting the approximation for small times described in Section A of S1 Appendix. Thus - keeping $dK=0$ and $d\tau=0$ - the sensitivity of Q_{ss} and P_{ss} to changes in r - with respect to the reference normal state r_n - is given by

$$dP_{ss} = \frac{K}{{r_n}^2\cdot\tau^2}\cdot dr \sim 4\cdot 10^{21} ATPeq\cdot dr \qquad \text{(S5)}$$

$$dQ_{ss} = \frac{K}{{r_n}^2\cdot\tau}\cdot dr \sim 3\cdot 10^{23} ATPeq h^{-1}\cdot dr \qquad \text{(S6)}$$

The actual change in P_{ss} and Q_{ss} can be inferred from Eqs. S5 and S6 with respect to the change in r (dr) for increasing malignancy of the neoplastic plasma cells (r_m) with respect to normal PCs (r_n) - as shown in the table below (and Fig 4).

Table A. Analytical sensitivity analysis for the single population model applied to PCs

$dr = r_m - r_n$	$0.04\cdot 10^{-2}\, h^{-1}$	$0.05\cdot 10^{-2}\, h^{-1}$	$0.08\cdot 10^{-2}\, h^{-1}$	$0.14\cdot 10^{-2}\, h^{-1}$
dP_{ss}	$0.16\cdot 10^{19} ATPeq\, h^{-1}$ ~ $0.03\cdot K/\tau$	$0.20\cdot 10^{19} ATPeq\, h^{-1}$ ~ $0.04\cdot K/\tau$	$0.32\cdot 10^{19} ATPeq\, h^{-1}$ ~ $0.06\cdot K/\tau$	$0.56\cdot 10^{19} ATPeq\, h^{-1}$ ~ $0.1\cdot K/\tau$
dQ_{ss}	$0.12\cdot 10^{21} ATPeq$ ~ $0.03\cdot K$	$0.15\cdot 10^{21} ATPeq$ ~ $0.04\cdot K$	$0.24\cdot 10^{21} ATPeq$ ~ $0.06\cdot K$	$0.42\cdot 10^{21} ATPeq$ ~ $0.1\cdot K$

C. Simulator as Python routine

The routine can be run as .py script once included the following libraries in a Python environment:

- numpy (https://numpy.org/doc/stable/user/index.html#user)
- matplotlib (https://matplotlib.org/stable/index.html)
- scipy (https://docs.scipy.org/doc/).

The actual parameter setting and aesthetics reproduces Fig 10 of the main text. It is straightforward to extend the method for the numerical sensitivity analysis to other model parameters.

```
#!/usr/bin/env python3
# -*- coding: utf-8 -*-

#importing python libraries
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp #method from scipy

#MODEL for two interacting stocks
def model_metabolism_interacting(t, z, K, r1, r2, T1, T2, a1, a2, f):

        Q1, Q2 = z #normal cells, cancer cells (first derivative)

        return [ r1*Q1*(1-Q1/K-f*Q2/K)-Q1/T1-a1*Q1*Q2,
        r2*Q2*(1-f*Q2/K-Q1/K)-Q2/T2-a2*Q1*Q2]

#SENSITIVITY to competition parameters AND REGIME SHIFTS
#SCENARIOS and model calibration
K=4.05e21                   #carrying capacity in ATP equiv , total cells in the niche
tau = 72/8760               #TURNOVER TIME FOR BIOSYNTHESIS same for both NORMAL AND CANCER: proteome turnover
time, biochemical constraint
T1 = T2 = tau
"""
#SENSITIVITY to changes in the growth rate of one population
#sensitivity analysis on neoplastic plasma cells phenotype spans biomedical observed value (REFs)
RGR2_sens = np.array([0.03, 0.04, 0.06, 0.07, 0.08, 0.1])*(8760/72)  #%/ANNO ,0.5,0.8,0.9
r2_sens=RGR2+1/T2
"""
#malignant plasmacells
RGR2 = 0.1/T2
r2 = RGR2 + 1/T2
#normal plasmacells
Q1ss_est=8e19               #(ATPeq) steady state normal PCs
r1 =1/(T1*(1-((Q1ss_est)/K)))  #intrinsic growth rate estimation
#RGR_1 = r1-1/T1            #correspondent RGR?
Q10 = Q1ss_est
eta = 0.4                   #thermodynamic efficiency of ATP production process: FIXED BUILDING BLOCK OF LIFE, from Stat
Mechanics
#SOLVER
Q10=K*(1-1/(r1*T1))
Q20=5e10                    #(ATPeq) first mutation, 1 cell in ATPeq
DT=80
#sensitivity to biochemical interaction strength , same order of magnitude to estimated from maximum power state Q1ss=Q2ss=K/2
a1_sens=np.array([0,1,10,100])*r1/K
a2_sens=np.array([0,1,1,1])*r2/K        #,1,10,100 #1,2,5
f=1                         #mass/material balance closure, conservative scenario, for f<1 PCs abrogate hierarchical control :
exceeds in the carrying capacity
t = np.linspace(0, DT, 100*DT)
Q1_sens = list(np.zeros(len(a1_sens)))  #change to RGR2_sens
Q2_sens = list(np.zeros(len(a2_sens)))
P1_sens = list(np.zeros(len(a1_sens)))
P2_sens = list(np.zeros(len(a2_sens)))
Jh_sens = list(np.zeros(len(a2_sens)))
```

```
for i in range(0,len(a2_sens)):
        sol_metabolismINT = solve_ivp(model_metabolism_interacting,

                [0, DT],                        #timespan

                [Q10, Q20],             #initial stock condition

                t_eval = t,             #impose the timestamp

                method='Radau',     #integration method: Radau

                args=(K, r1, r2, T1, T2, a1_sens[i], a2_sens[i], f), #definition of the constants

                dense_output=True)              #True = computes continuous solution
  #solutions
        Q1_sens[i]=sol_metabolismINT.sol(t)[0]
        Q2_sens[i]=sol_metabolismINT.sol(t)[1]
        P1_sens[i]=r1*Q1_sens[i]*(1-Q2_sens[i]/K-f*Q2_sens[i]/K)
        P2_sens[i]=r2*Q2_sens[i]*(1-Q1_sens[i]/K-f*Q2_sens[i]/K)
        """
        #sensitivity to phenotype, substitute
        #P2_sens[i]=r2_sens[i]*Q2_sens[i]*(1-Q1_sens[i]/K-f*Q2_sens[i]/K)
        """
        Jh_sens[i]=P1_sens[i]/eta + P2_sens[i]/eta

#P1, P2, power in ATPeq/year - Jh, heat flows kJ/year
#DYNAMICS
fig, ax = plt.subplots(figsize=(9,4.5),dpi=400)#,dpi=400
#power flows
ax.plot(t,P2_sens[3], color="crimson",ls=":")
ax.plot(t,P1_sens[3], color="tab:blue",ls=":")
ax.plot(t,P2_sens[2], color="crimson",ls="-.")
ax.plot(t,P1_sens[2], color="tab:blue",ls="-.")
ax.plot(t,P2_sens[1], color="crimson",ls="--")
ax.plot(t,P1_sens[1], color="tab:blue",ls="--")
ax.plot(t,P2_sens[0], color="crimson")
ax.plot(t,P1_sens[0], color="tab:blue")
ax.set_ylim(-0.1*Q1ss_est/(eta*T1),Q1ss_est/(eta*T1)+0.3*Q1ss_est/(eta*T1))#+0.1*Q1ss_est/T1
ax.set_xlim(-1,5)
#heat flows
ax2 = ax.twinx()
ax2.plot(t,Jh_sens[0], color="k")
ax2.plot(t,Jh_sens[1], color="k",ls="--")
ax2.plot(t,Jh_sens[2], color="k",ls="-.")
ax2.plot(t,Jh_sens[3], color="k",ls=":")
ax2.set_ylim(-0.1*Q1ss_est/(eta*T1),Q1ss_est/(eta*T1)+0.3*Q1ss_est/(eta*T1))#+0.1*Q1ss_est/T1
ax2.set_yticklabels([r"0",r" ",r"$0.97$",r"$2.4$"],fontsize="small")
ax2.set_ylabel(r'$J_h$ $(\frac{k·J}{year})$')
ax2.set_yticks(np.array([0, P2_sens[0][0], P1_sens[0][0],Jh_sens[0][0]]))#$5·10^{10}$
#figure aestethics
ax.set_yticks(np.array([0, P2_sens[0][0], P1_sens[0][0],Jh_sens[0][0]]))#$5·10^{10}$
ax.set_yticklabels([r"0",r" ",r"$9.7·10^{21}$",r"$2.4·10^{22}$"],fontsize="small")
ax.grid(True,axis="y")
ax.set_ylabel(r'$P$ $(\frac{ATPeq}{year})$')
ax.set_xlabel(r'$t$ $(years)$')
ax.text(0,2.6e22,r"$J_h$",fontsize=15)
ax.text(0,1.2e22,r"$P_1$",fontsize=15)
ax.text(0,1e21,r"$P_2$",fontsize=15)
ax2.legend([r"$\alpha_2=\alpha_1=0$",r"$\alpha_2 \approx \alpha_1$", r"$\alpha_2 \approx 10·\alpha_1$", r"$\alpha_2 \approx
100·\alpha_1$"], shadow=False, loc="center right", fontsize="small",framealpha=0) #,"","","",""
ax.set_xticklabels([r" ",r"$0$",r"$1$",r"$2$",r"$3$",r"$4$",r"$5$"],fontsize="small")

###
x=3
t1 = Q1_sens[x]/(P1_sens[x]-Q1_sens[x]/T1-a1_sens[x]*Q1_sens[x]*Q2_sens[x])
plt.plot(t,t1)
plt.xlim(-1,5)
```

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