Mathematical models of chronic lymphocytic leukemia

- Introduction to CLL
- Ibrutinib therapy – understanding the kinetics
- Calculating personalized treatments

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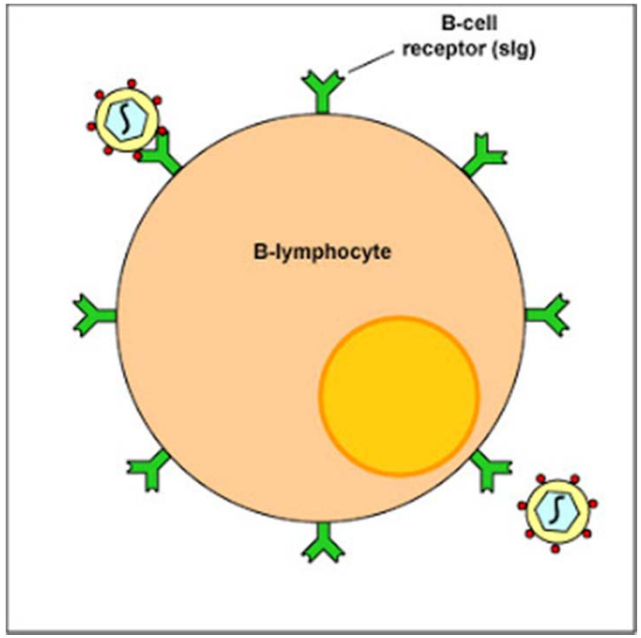
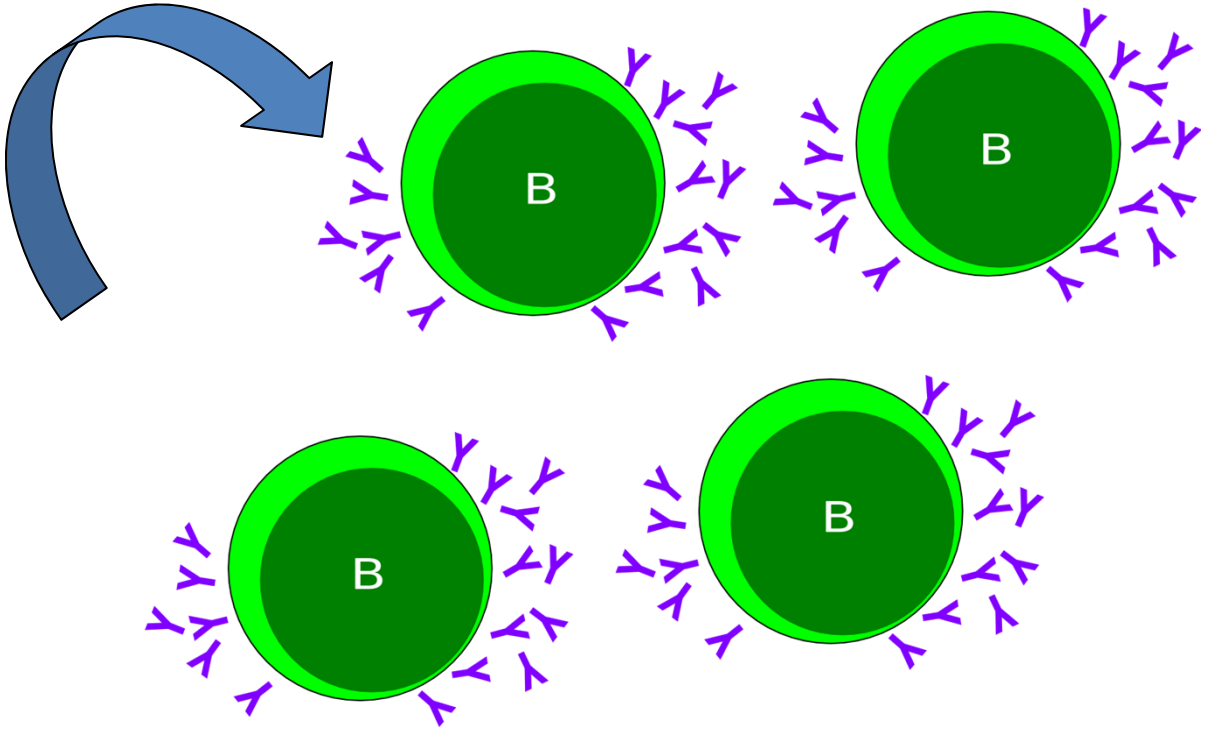
Intro to CLL

- most common type of leukemia
- accumulation of small B lymphocytes with mature appearance
- most patients are diagnosed without symptoms during routine blood tests
- Upon diagnosis, a “wait and see” approach is followed.
- Treatment only initiated if certain conditions are met
  =>Rai and Binet staging; blood counts, doubling times of cells, etc
- Over the last years, patients are treated with a combination of chemotherapy (e.g. fluradabine, cyclophosphamide) and antibody therapy (rituximab)

Cells of origin

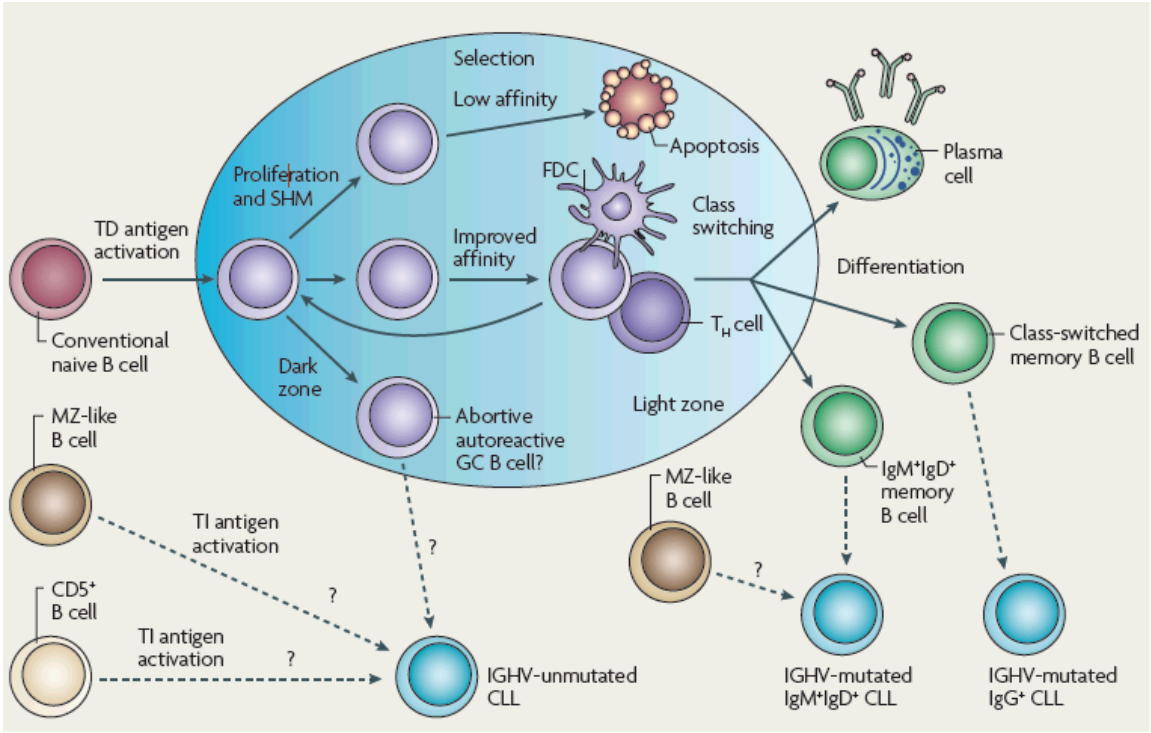


Resting B cell becomes activated by pathogen



Activated B cell proliferates and secretes antibody

Cells of origin



"unmutated"
worse prognosis

"mutated"
better prognosis

heterogeneity

del 13q: Deletion of long arm of chromosome 13, is the most common abnormality (50%). Best prognosis, some never need treatment

Trisomy 12: 20-25% of patients, have intermediate prognosis

del 11q: Deletion of long arm of chromosome 11, relatively poor prognosis, because deletion targets the ATM gene. Occurs in 5-10% of cases

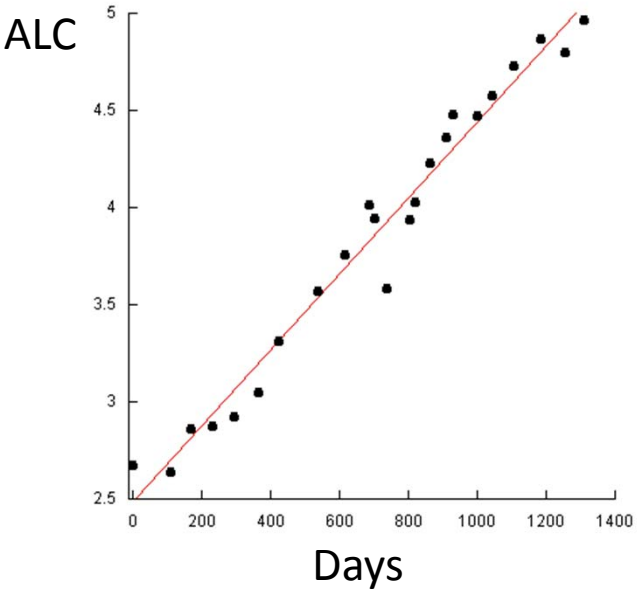
del 17p: deletion of part of short arm of chromosome 17. Poorest prognosis because it inactivates p53. (5-10% of cases)

Kinetics & Therapy of CLL

- Growth kinetics before treatment

- Kinetics during targeted therapy

Growth kinetics



- growth tends to be exponential in the long term
- you can feed heavy water to patients to label cells
- dynamics of label uptake and dilution allows you to estimate the division rate of cells
- knowing the overall growth rate and the division rate of cells allows us to estimate the death rate of cells.

- Messmer et al 2005
- Our own work in progress

about 0.5% of cells die per day

Therapy

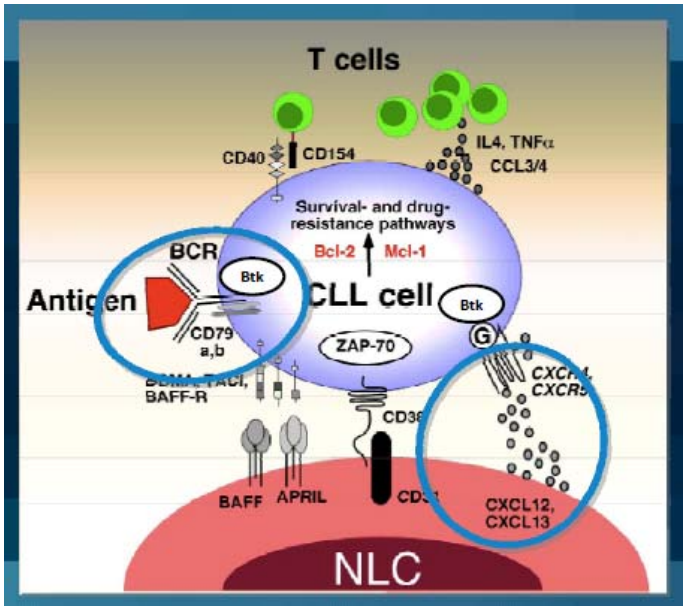
up to 2014, the standard was “chemo-immunotherapy”
=> good results, except for more virulent
disease types, e.g. del 17p

this is still the case, but things are changing

Targeted treatment approaches are emerging.

Ibrutinib

- Previously called PCI-32765
- First Bruton tyrosine kinase (BTK) inhibitor
- acts via specific binding to a cysteine residue in the BTK kinase domain
- inhibits BTK phosphorylation and its enzymatic activity
- Clinically active through:
  - induction of cell death
  - inhibition of proliferation
  - inhibition of tissue homing



Approved 13 Nov 2013 (Imbruvica)

Treatment response to Ibrutinib

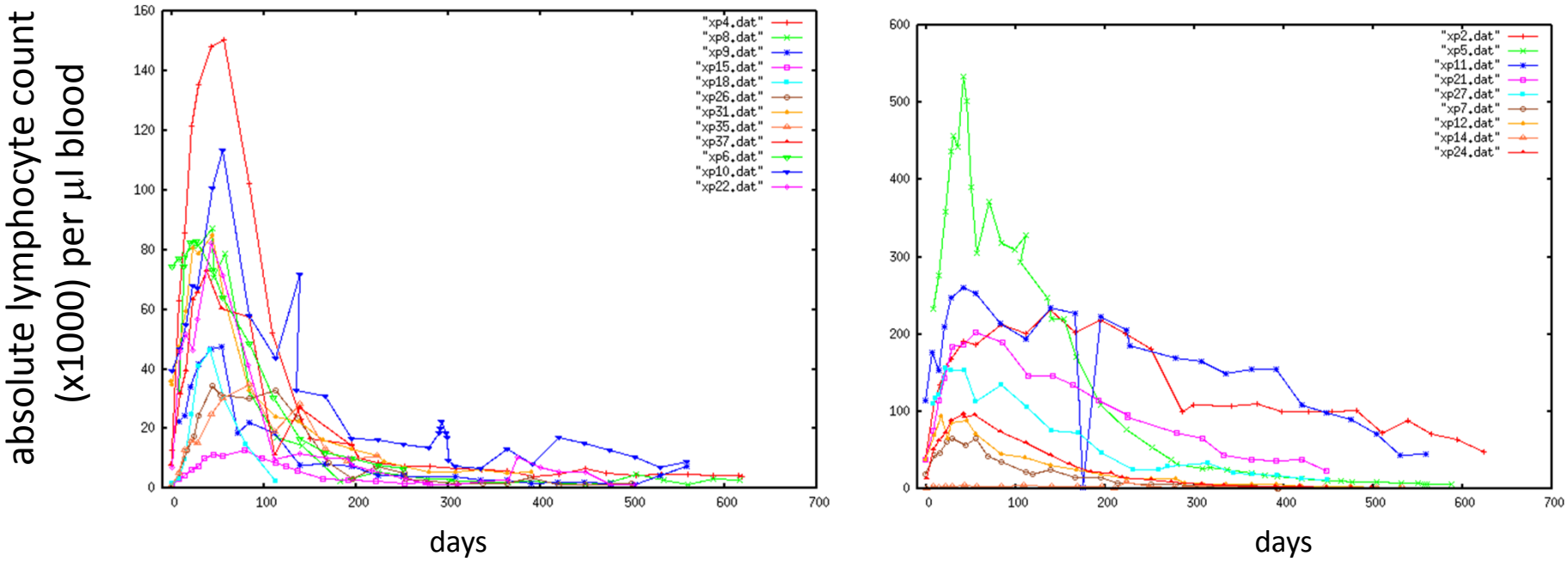
blood

Prepublished online May 14, 2014;
doi:10.1182/blood-2014-02-554220

Kinetics of chronic lymphocytic leukemia (CLL) cells in tissues and blood during therapy with the BTK inhibitor ibrutinib

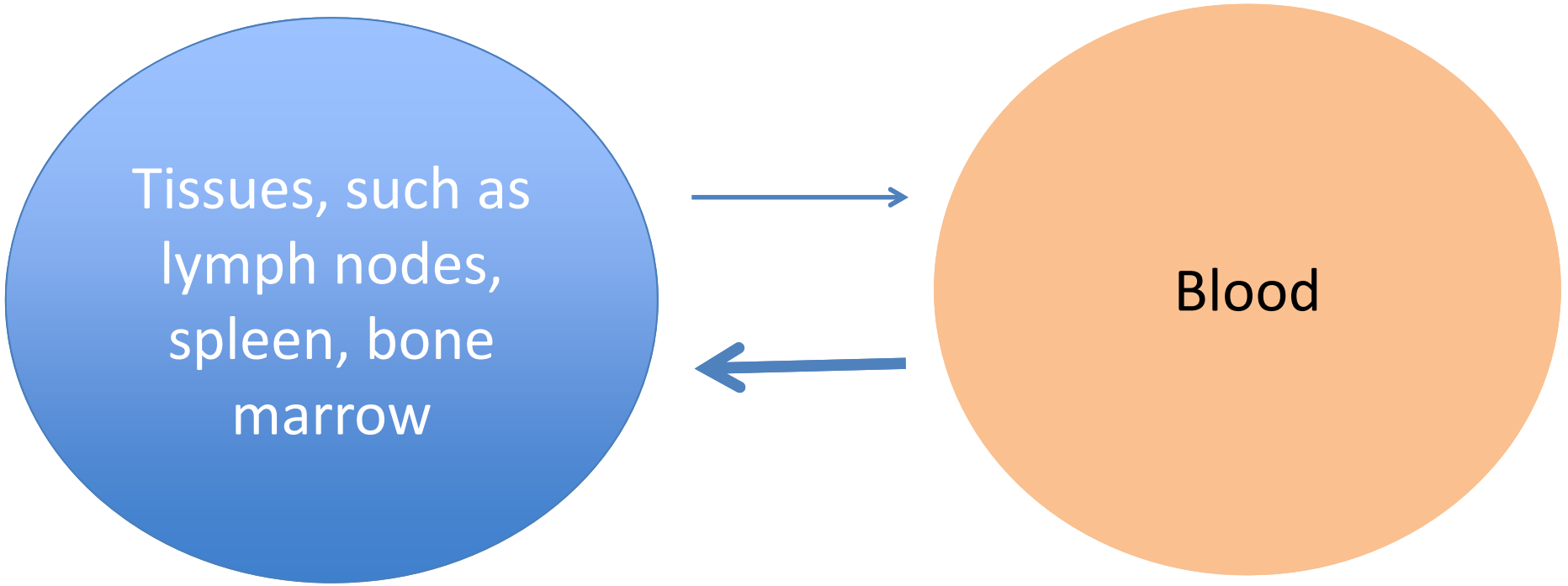
Dominik Wodarz, Naveen Garg, Natalia L. Komarova, Ohad Benjamini, Michael J. Keating, William G. Wierda, Hagop Kantarjian, Danelle James, Susan O'Brien and Jan A. Burger

CLL response to Ibrutinib
(treatment start at day 0)



Every patient shows a temporary phase of **lymphocytosis**, where the number of CLL cells in blood increases up to a peak, before eventually declining.

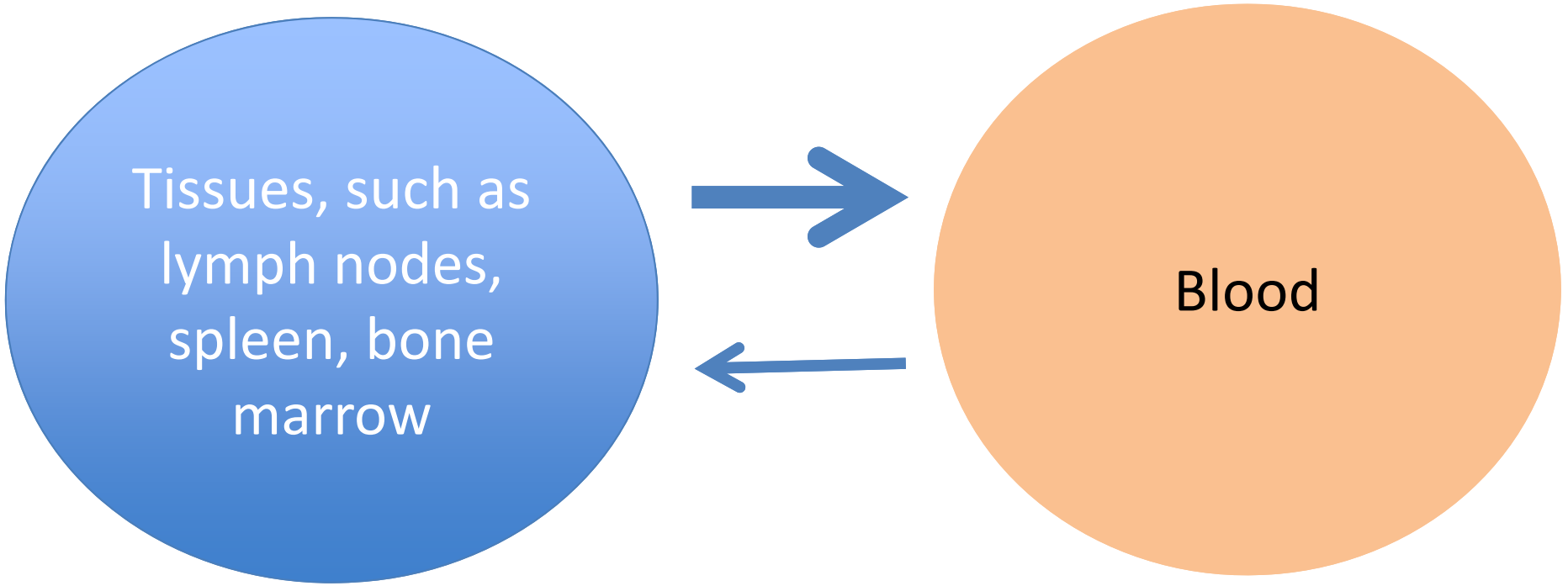
Compartments



Action, i.e. division and growth, most cells here =>Microenvironment

No action small fraction of tumor

Ibrutinib



Action, i.e. division and growth, most cells here =>Microenvironment

No action small fraction of tumor

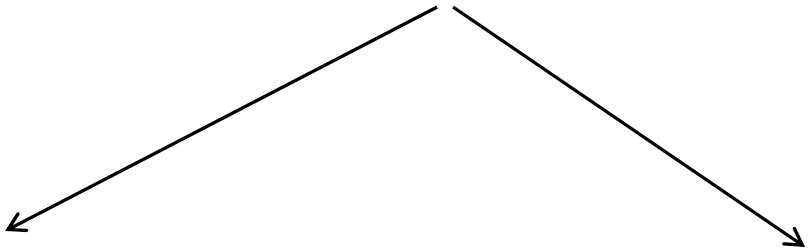
Question

What does this lymphocytosis mean?

Cells in the blood only tip of ice berg

Most action occurs in tissues (lymph nodes, spleen, bone marrow)

Ibrutinib disrupts tissue microenvironment, thus cells re-distribute to blood



Do most cells simply shift between compartments?

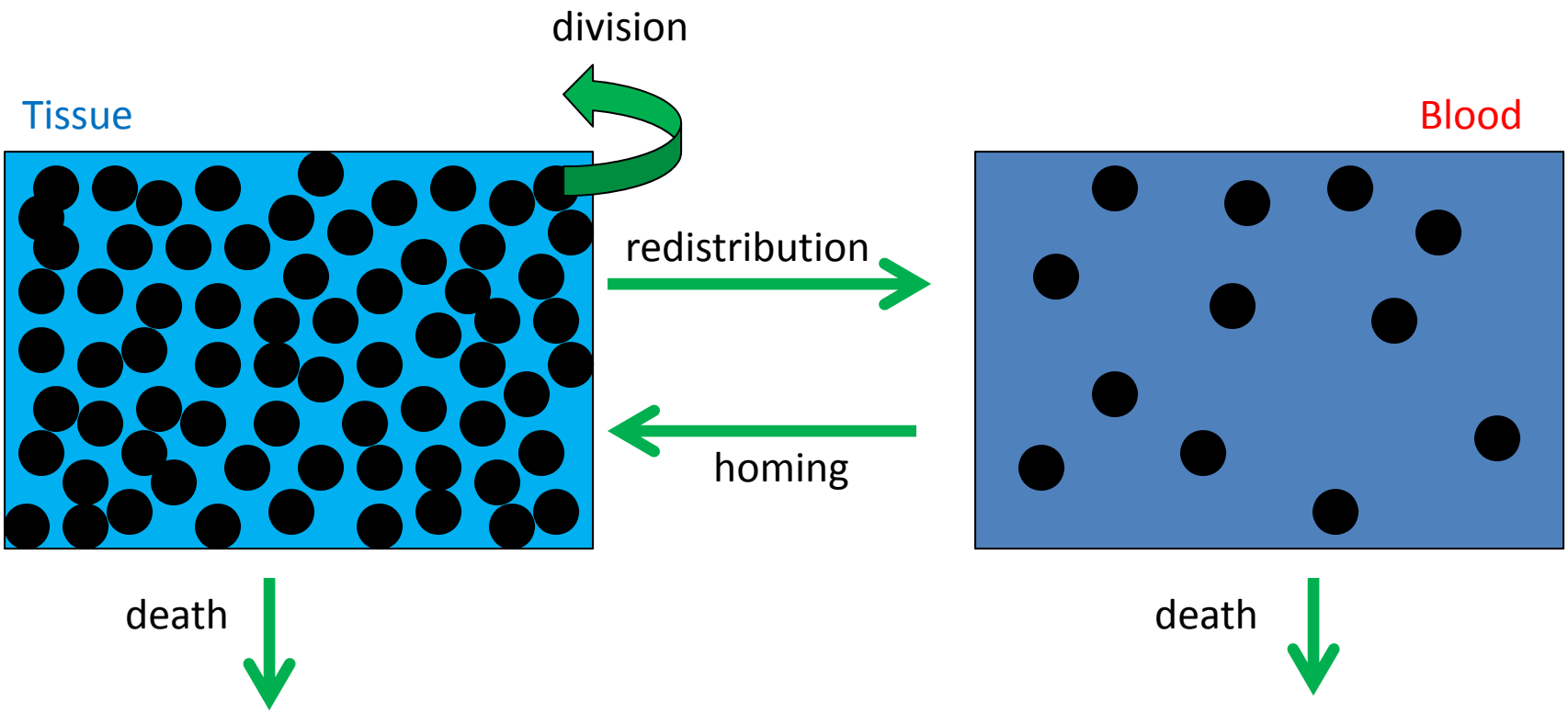
=> drug not very effective

Do most tissue cells die and only a minority redistribute?

=> drug effective

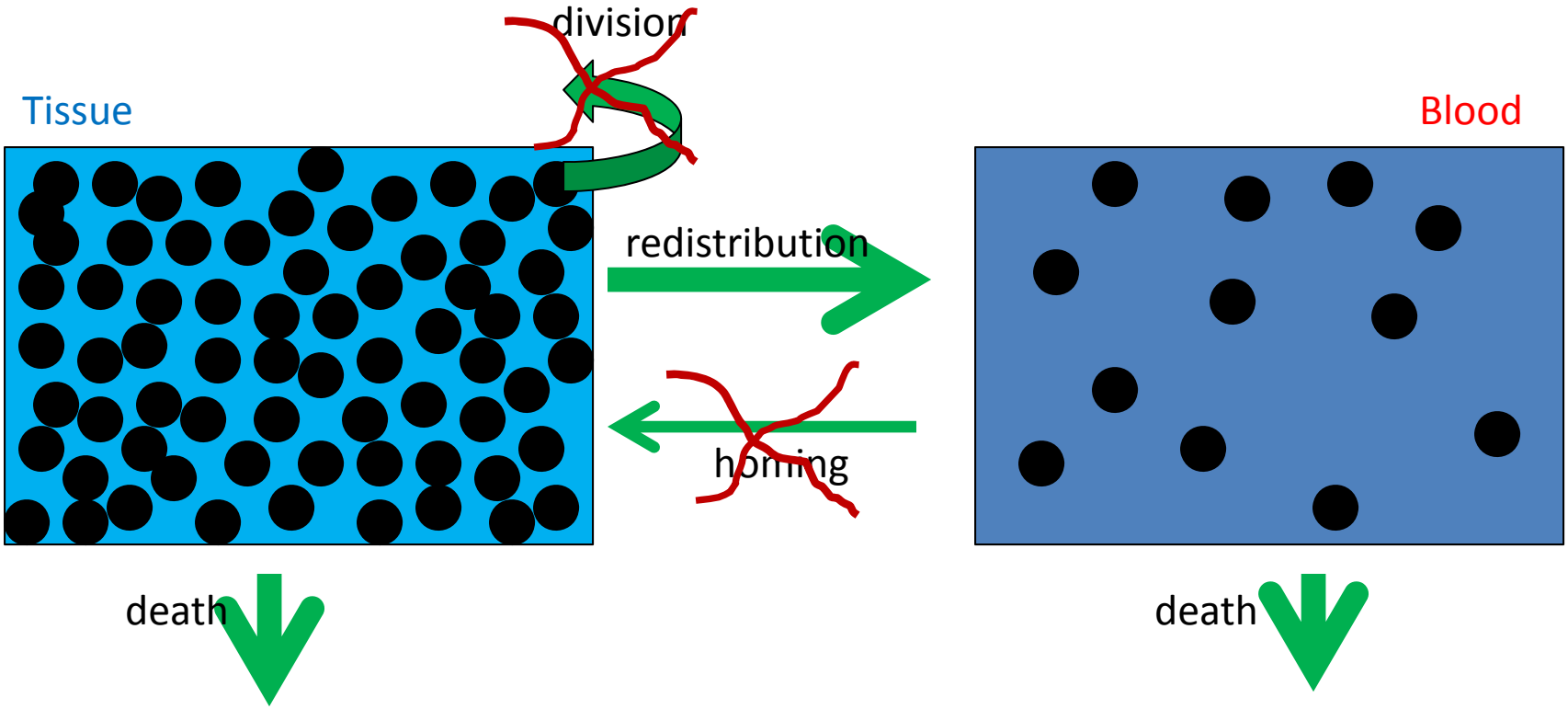
Mathematical model

We considered a two-compartment model for CLL dynamics:



Mathematical model

Treatment:



Mathematical model

m = rate of redistribution

d_1= CLL cell death rate in tissue

d_2 = CLL cell death rate in blood

c = factor to account for the observation that CLL cells stabilize at low levels in the long term

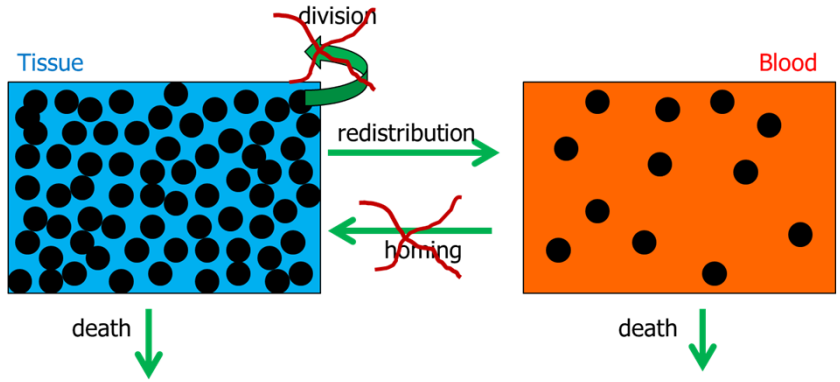
nodal response rate: $\alpha = m + d_1$

idea: fit model to treatment data and estimate the parameters

$$\frac{dx}{dt} = -mx - d_1(x - c)$$

$$\frac{dy}{dt} = mx - d_2 y$$

Treatment:



Model

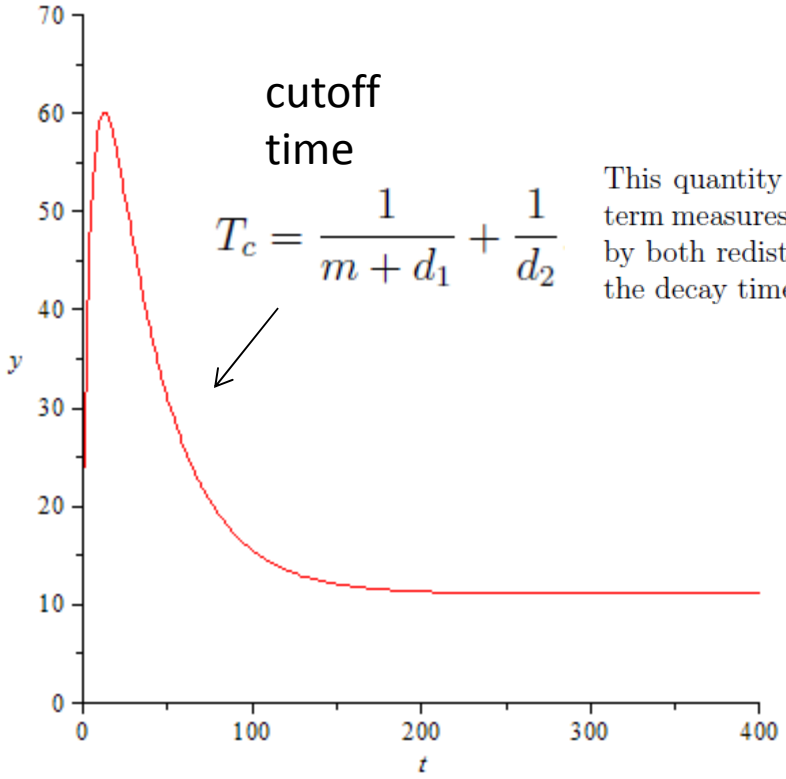
Aims:

- estimate crucial parameters
- calculate the percentage of pre-treatment tissue tumor burden that redistributes into the blood

Model

Relative number of cells redistributed from tissue to blood:

$$Z(t) = \frac{\int_0^t mx(t')\,dt'}{x_0} = \frac{m}{\alpha x_0}\left((x_0 - C_x)(1 - e^{-\alpha t}) + \alpha C_x t\right). \qquad (11)$$



cutoff time

$$T_c = \frac{1}{m + d_1} + \frac{1}{d_2}$$

This quantity is a composite of two characteristic times of decay: the first term measures the decay-time of CLL lymphocytes in tissues (and it is defined by both redistribution and death processes), and the second term measures the decay time in blood, defined uniquely by the death rate d_2.

Tumor stabilizes due to parameter *c*

this phase is not interesting. Here *Z* grows linearly in time because of remaining equilibirum level of CLL cells in tissue

Model fitting

Model contains 2 variables:

cells in tissues

$$\frac{dx}{dt} = -mx - d_1(x - c)$$

cells in blood => absolute lymphocyte counts

$$\frac{dy}{dt} = mx - d_2 y$$

Model fitting

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cells in blood => absolute lymphocyte counts

$$\frac{dy}{dt} = mx - d_2 y$$

Fitting

The solution reads

$$x(t) = C_x + (x_0 - C_x)e^{-\alpha t}, \tag{9}$$

$$y(t) = \frac{mx_0}{d_2 - \alpha}e^{-\alpha t} + \left(y_0 - \frac{mx_0}{d_2 - \alpha} - C_y\right)e^{-d_2 t} + C_y. \tag{10}$$

It turns out that apart from the solution just described, there is always a second solution which yields exactly the same fit, with

$$\hat{\alpha} = d_2, \quad \hat{d}_2 = \alpha, \tag{12}$$

$$\hat{C}_y = C_y, \quad \hat{y}_0 = y_0, \quad m\hat{x}_0 = mx_0 + (y_0 - C_y)(d_2 - \alpha). \tag{13}$$

This duality of solution does not allow one to determine the parameters

Solution

We need to know the number of CLL cells in tissue at least at two time points

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We need to know the number of CLL cells in tissue at least at two time points

Use radiological data available for a subset of patients to estimate the number of CLL cells in tissue

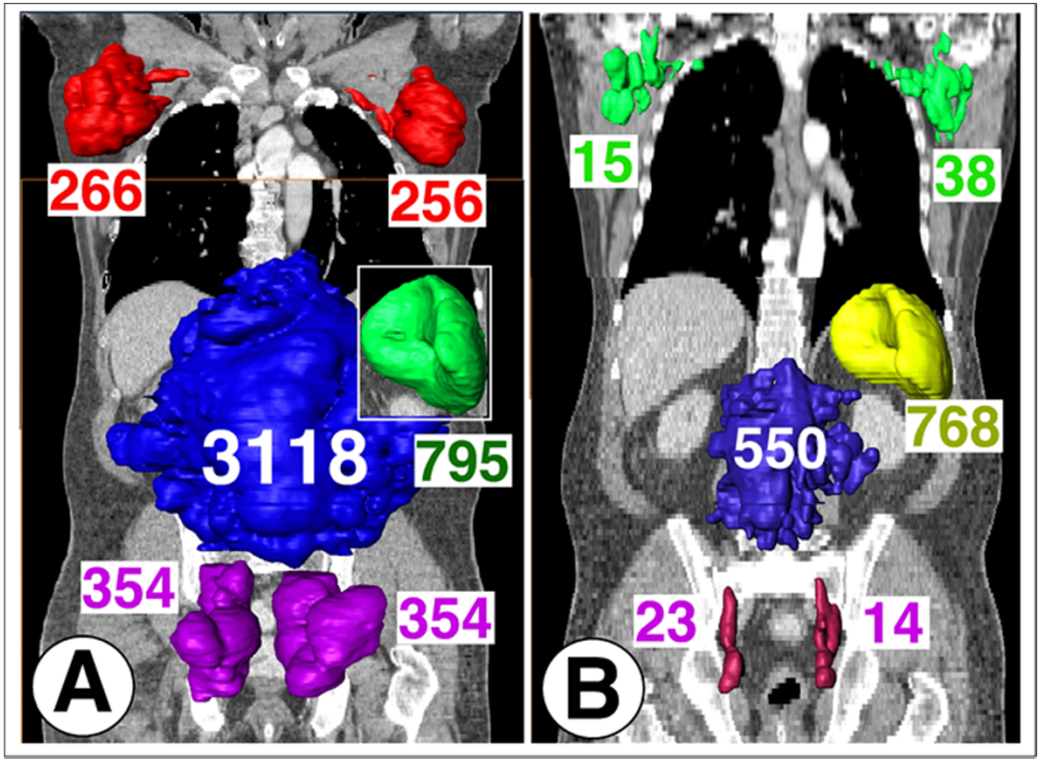
Solution

We need to know the number of CLL cells in tissue at least at one time point

Use radiological data available for a subset of patients to estimate the number of CLL cells in tissue

The volume of lymphoid tissues and the spleen was quantified by computed tomography (CT) scans, and this was used to estimate the number of CLL cells in the tissues

Volumetric Analysis



Volumetric analyses of CLL lymph node and spleen manifestation (A) before and (B) during therapy with ibrutinib.

Depicted are CT images from a representative CLL patient from our series with superimposed reconstruction of main areas of CLL involvement, highlighted in color. The volumes of the axillary (red), intra-abdominal (blue), inguinal (purple) and spleen (green, yellow) disease manifestations are displayed next to each involved area.

Volumetric analysis done for 3 time points: one before treatment, two during treatment

Model fitting

Model contains 2 variables:

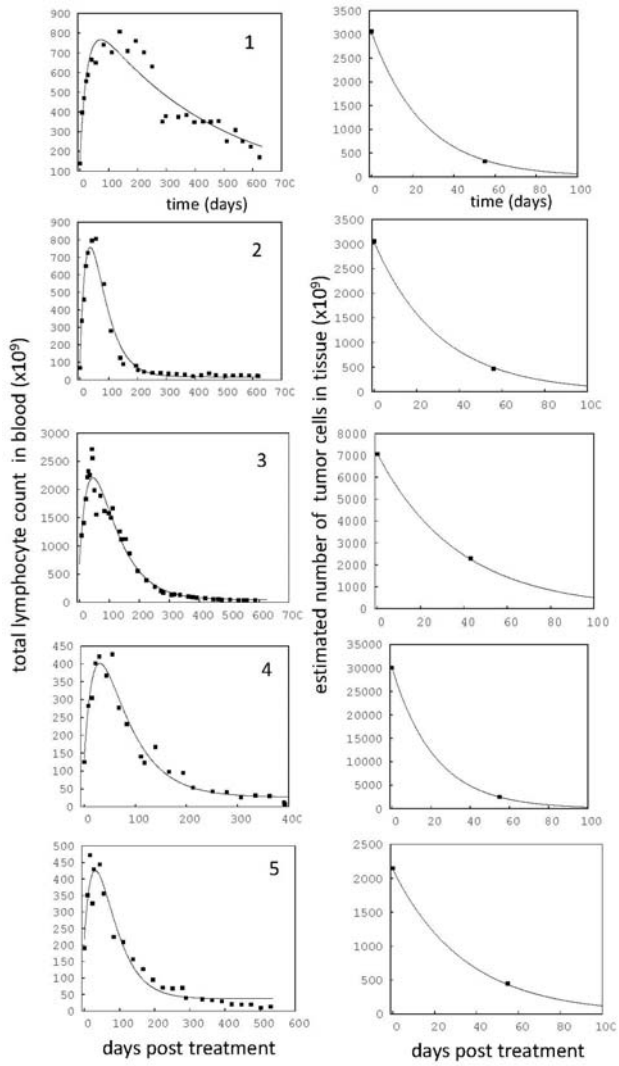
- cells in tissues

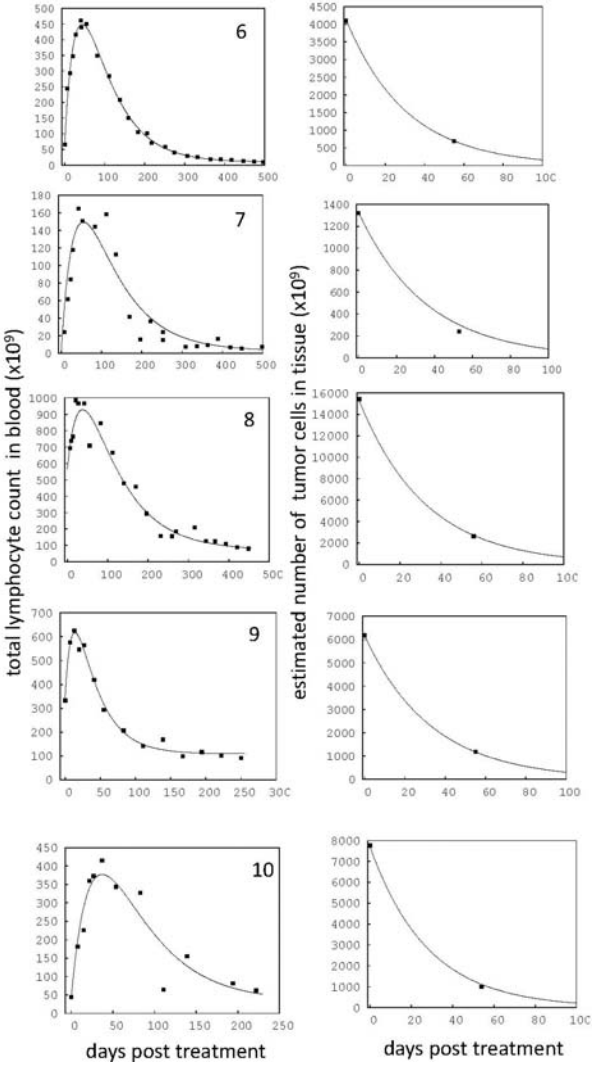
$$\frac{dx}{dt} = -mx - d_1(x - c)$$

- cells in blood => absolute lymphocyte counts

$$\frac{dy}{dt} = mx - d_2 y$$

Fitting


1
2
3
4
5
time (days)
time (days)
total lymphocyte count in blood (x10⁹)
estimated number of tumor cells in tissue (x10⁹)
days post treatment
days post treatment


6
7
8
9
10
total lymphocyte count in blood (x10⁹)
estimated number of tumor cells in tissue (x10⁹)
days post treatment
days post treatment

Parameter Estimates

patient	d_2 (d^{-1})	d_1 (d^{-1})	m (d^{-1})	α (d^{-1})	x_0 ($x10^9$)	y_0 ($x10^9$)	% redistr.
1	0.002	0.027	0.0096	0.037	3034	153	25.9
2	0.022	0.015	0.0177	0.033	3064	58	50
3	0.014	0.012	0.0146	0.026	7044	674	52.6
4	0.016	0.047	0.0009	0.047	30209	120	1.9
5	0.018	0.022	0.0095	0.032	2143	217	29.4
6	0.014	0.027	0.0061	0.033	4083	73	18.2
7	0.010	0.022	0.0056	0.028	1294	3	19.6
8	0.011	0.032	0.0023	0.034	15452	521	6.9
9	0.047	0.033	0.0088	0.042	6156	358	19.3
10	0.018	0.035	0.0034	0.039	7711	38	8.8
average	**0.017**	**0.027**	**0.008**	**0.035**	**8019**	**221**	**23.3**
st. dev.	**0.011**	**0.010**	**0.005**	**0.006**	**8799**	**226**	**17.0**

d_2 = death rate of CLL cells in blood;

d_1 = death rate of CLL cells in tissue;

m = rate of redistribution of tissue cells to blood;

α = overall nodal decline rate, i.e. rate at which cells disappear from the tissue due to redistribution + death, i.e. $\alpha=m+d_1$;.

x_0 = total body number of CLL cells in tissue;

y_0 = total body number of CLL cells in blood;

% redistr = % of pre-treatment tissue tumor burden that is redistributed.

Death rates

In tissue: $d_1 = 0.027 \pm 0.01\ days^{-1}$

2.7% ± 0.99% of the cells die per day in tissue

In blood: $d_2 = 0.017 \pm 0.012\ days^{-1}$

1.7% ± 1.1% of the cells die per day in the blood

Death rates

In tissue: $d_1 = 0.027 \pm 0.01\ days^{-1}$

2.7% ± 0.99% of the cells die per day in tissue

treatment increases death rate 5-fold

In blood: $d_2 = 0.017 \pm 0.012\ days^{-1}$

1.7% ± 1.1% of the cells die per day in the blood

treatment increases death rate 3-fold

Previous estimate in the absence of treatment:

0.5% of cells died per day

Death rates vs redistribution rate

In tissue: $d_1 = 0.027 \pm 0.01\ days^{-1}$

2.7% ± 0.99% of the cells die per day in tissue

In blood: $d_2 = 0.017 \pm 0.012\ days^{-1}$

1.7% ± 1.1% of the cells die per day in the blood

Redistribution rate: $m = 0.008 \pm 0.005\ days^{-1}$

Death rates vs redistribution rate

In tissue: $d_1 = 0.027 \pm 0.01\ days^{-1}$

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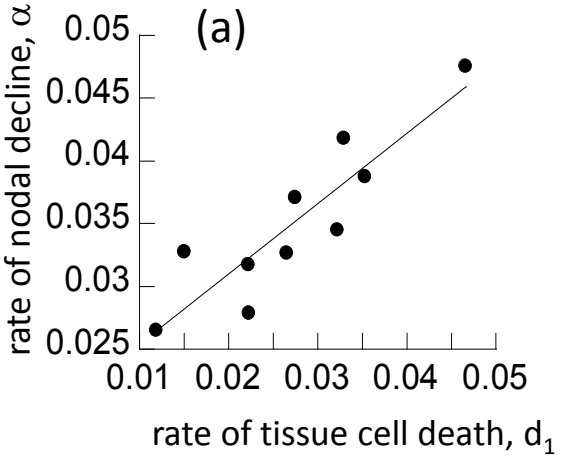
In blood: $d_2 = 0.017 \pm 0.012\ days^{-1}$

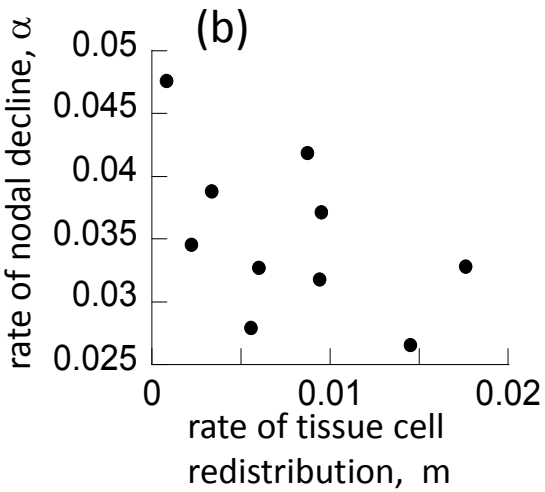
1.7% ± 1.1% of the cells die per day in the blood

Redistribution rate: $m = 0.008 \pm 0.005\ days^{-1}$

The percentage of the tissue CLL cell population that was re-distributed into the blood was **23.3 ± 17%.**

Nodal decline driven by cell death rather then redistribution





(a) There is a significant correlation between the rate of nodal decline and the death rate of cells in tissue (p=0.0005).

(b) There is no significant correlation between the rate of nodal decline and the redistribution rate of CLL cells.

Treatment Kinetics -summary

- Ibrutinib causes a substantial amount of cell death in tissue
- Lymphocytsis only represents a relatively small fraction of total tissue tumor burden
- Treatment can be considered effective

=> Parameters can be measured in individual patients

=> towards personalized prediction of treatment outcomes.

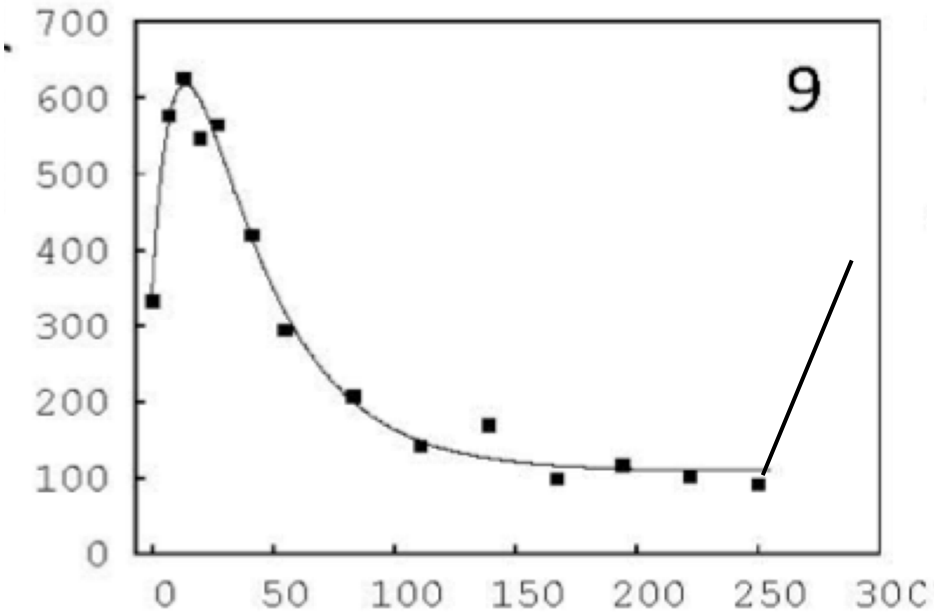
Evolutionary Dynamics of Drug Resistance

PNAS

Evolution of ibrutinib resistance in chronic lymphocytic leukemia (CLL)

Natalia L. Komarova[a,b,1], Jan A. Burger[c], and Dominik Wodarz[a,b]

[a]Department of Mathematics and [b]Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697; and [c]Department of Leukemia, MD Anderson Cancer Center, Houston, TX 77230



Resistance mechanisms

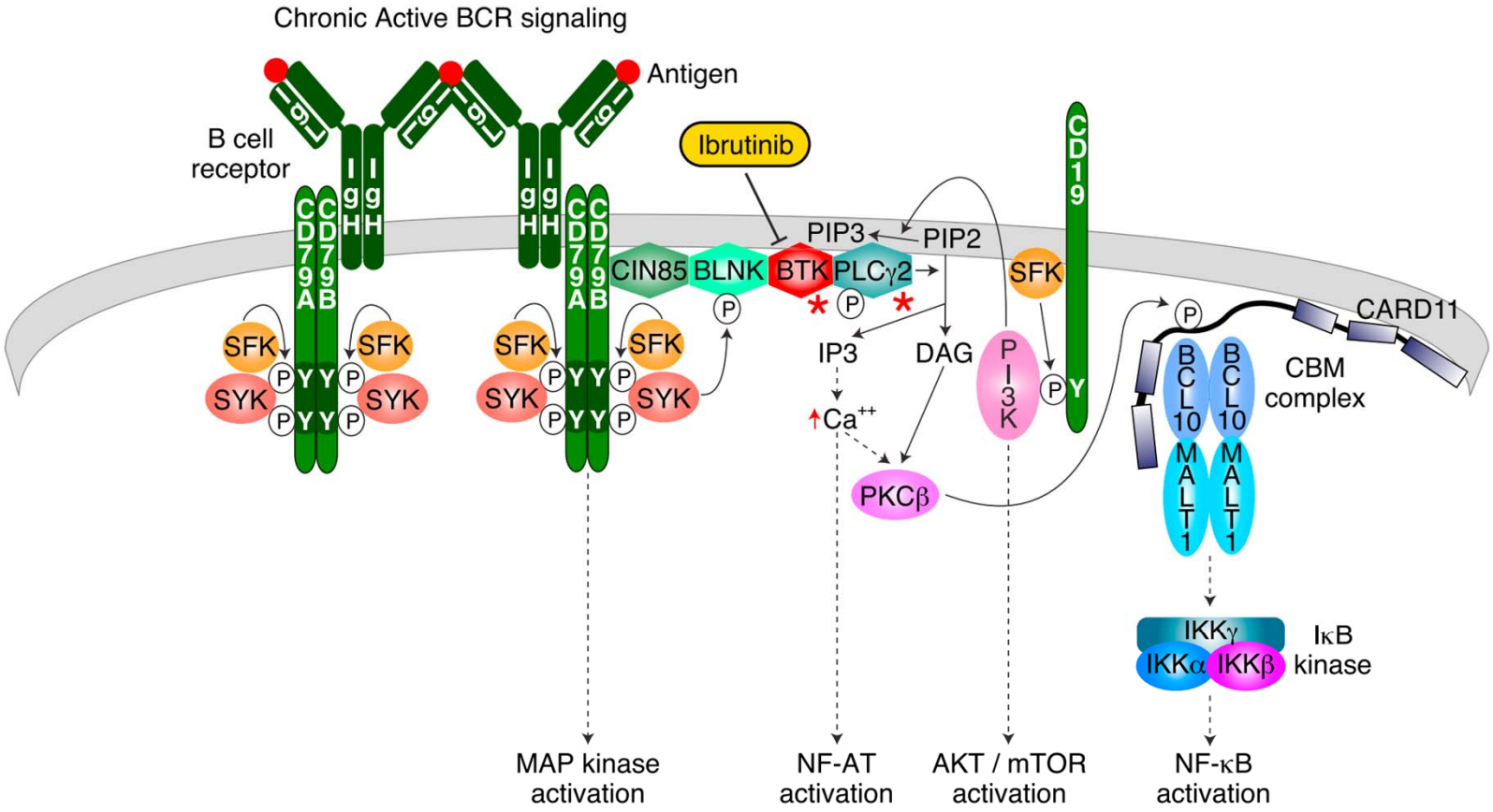


Figure 1. B Cell Receptor Signaling in Malignant B Cells

Chronic active BCR signaling is shown. Ibrutinib is shown to inhibit BTK. Red asterisks denote signaling effectors that are the target of ibrutinib resistance mutations in CLL patients.

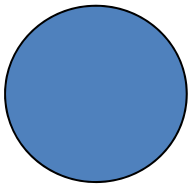
Question

- Can we plug in the measured parameters in order to predict the time until resistant mutants contribute to disease relapse?

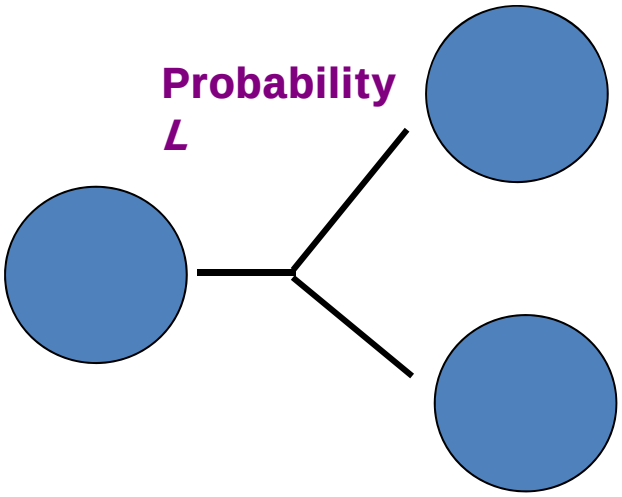
- I.e. can we predict how long ibrutinib monotherapy can maintain control of the disease?

Mathematical model – stochastic birth death process

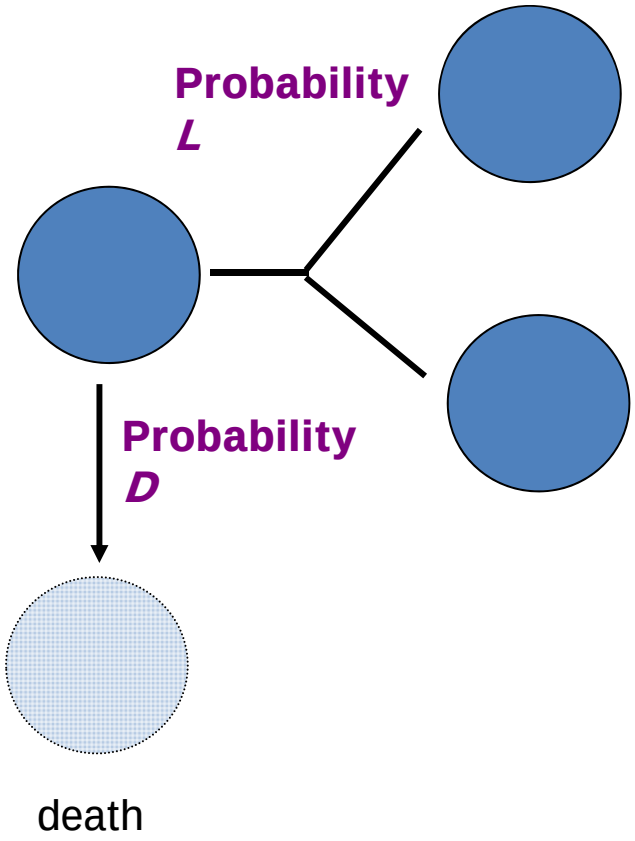
cancer cell



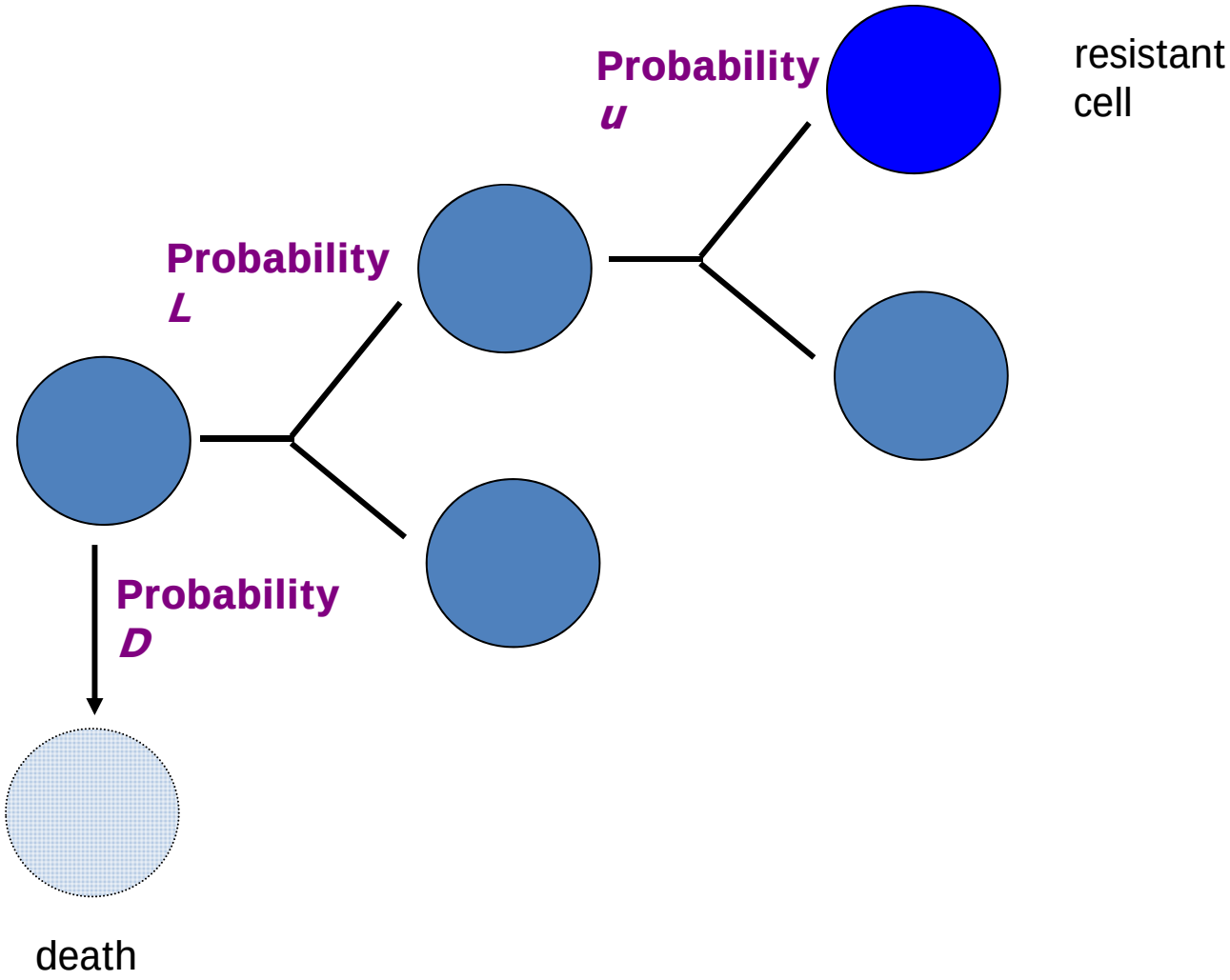
Mathematical model



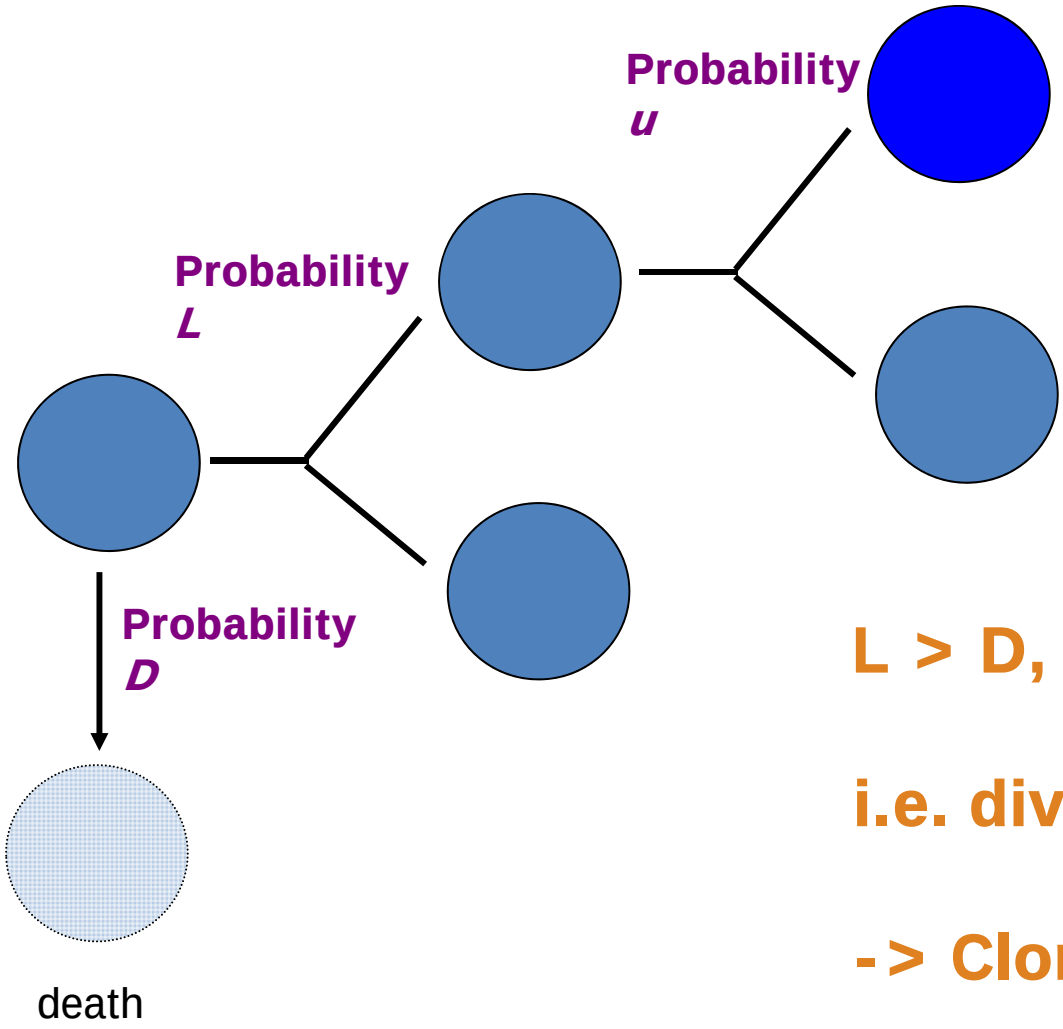
Mathematical model



Mathematical model



Mathematical model – growth phase

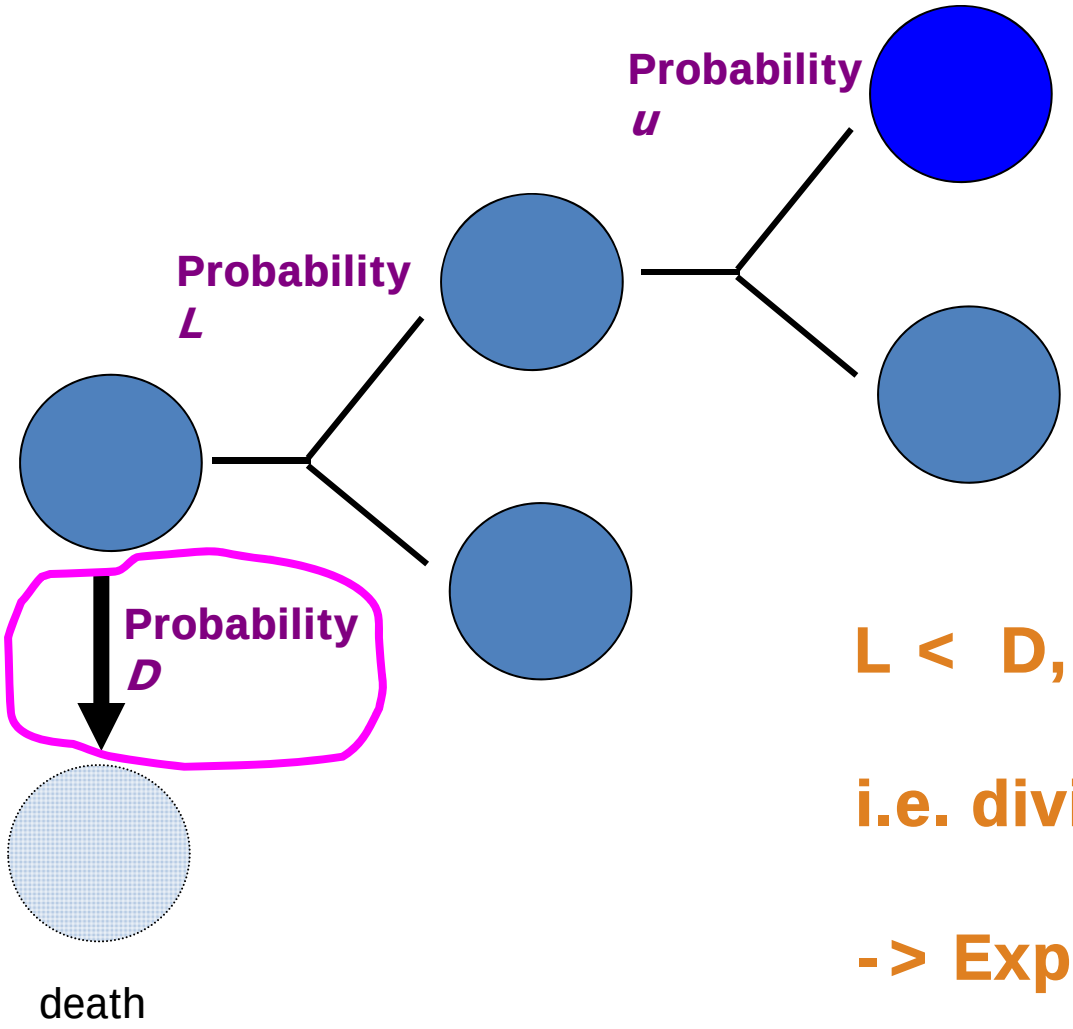


L > D,

i.e. division rate > death rate

-> Clonal Expansion

Mathematical model – treatment phase



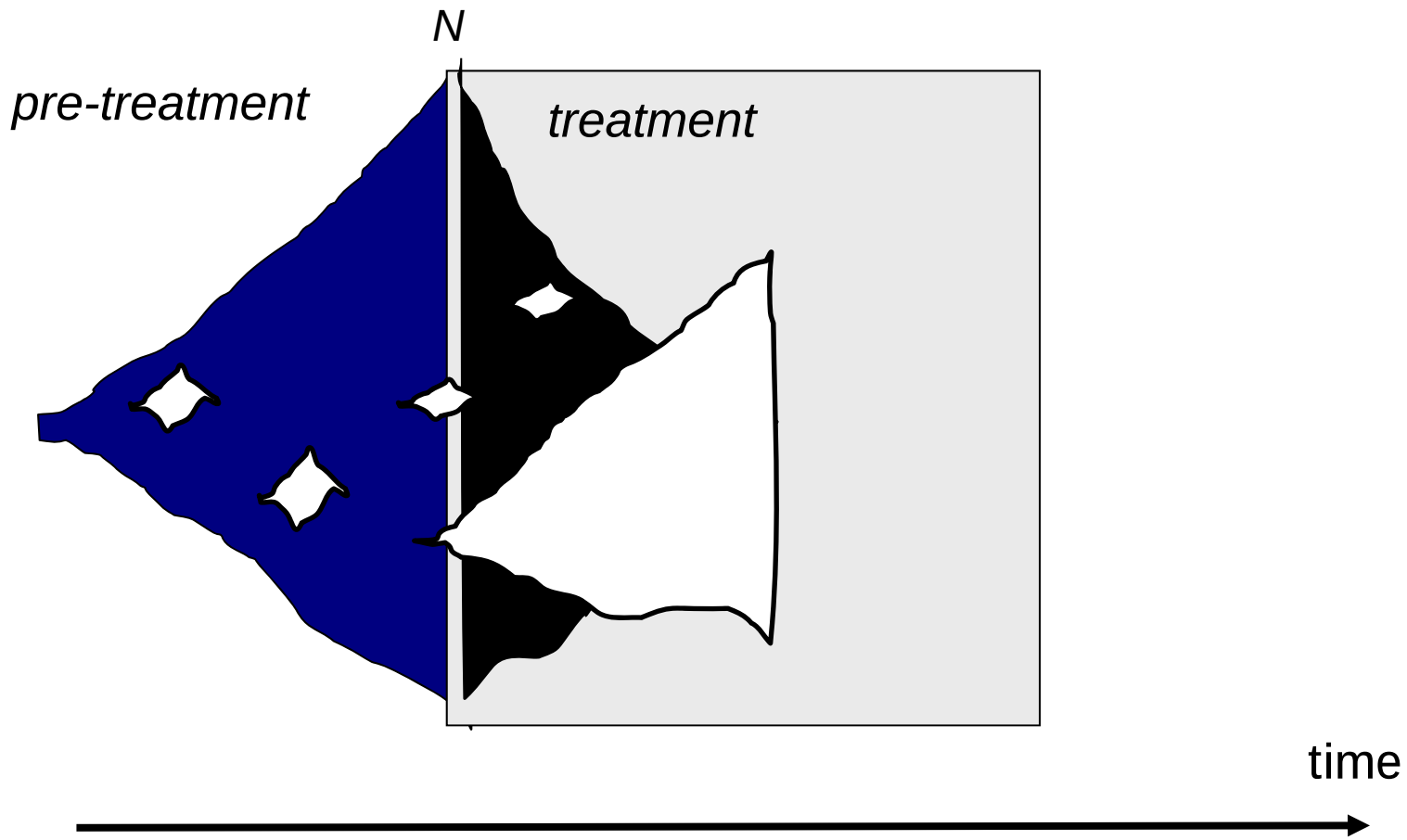
L < D,

i.e. division rate < death rate

-> Exponential Decline

Principles of model

(ii) with resistance

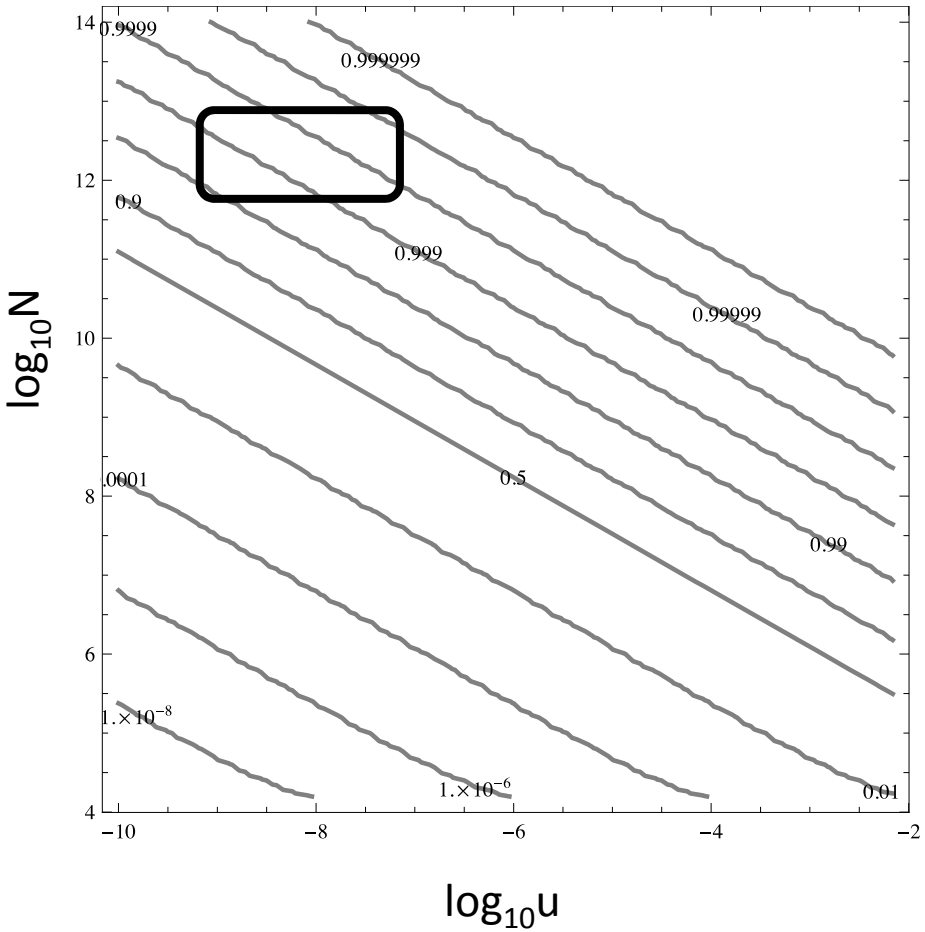


Virtual patients

Parameter estimates have been obtained from only a limited number of patients

A population of 1000 artificial “patients” is simulated with parameters randomly drawn from the experimentally available bounds

First result: Resistant mutants are almost certainly present before the start of therapy



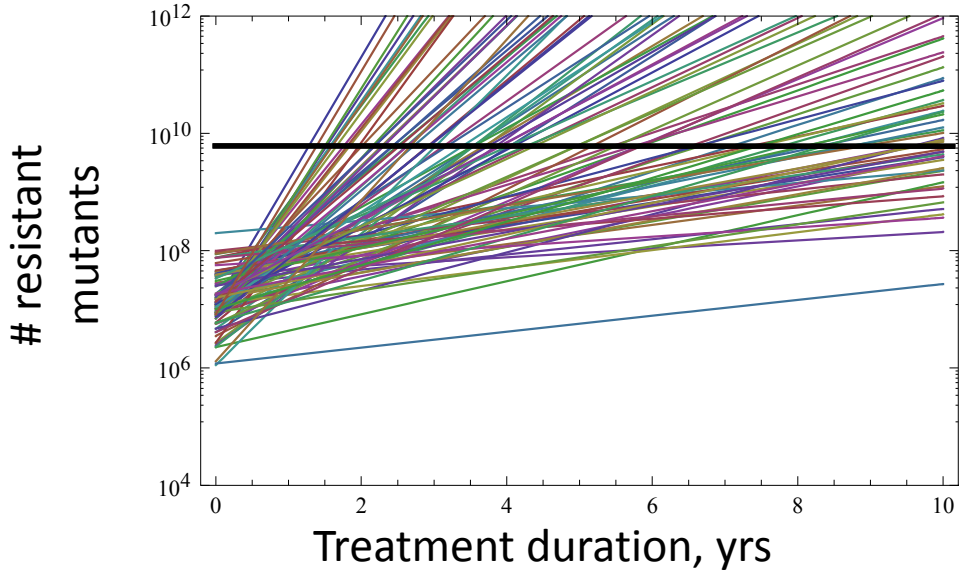
Probability of having a mutant in a colony at detection

Number of CLL cells in tissue is 10^{12}-10^{13}

Mutation rate is 10^{-9}-10^{-8}

Drug resistant cells are almost certain to exist before detection

Heterogeneity of patient populations



- Although resistance is predicted to be present with certainty, its dynamics are very different for different patients

- The only variables are CLL growth rates and population size at detection

Predictions

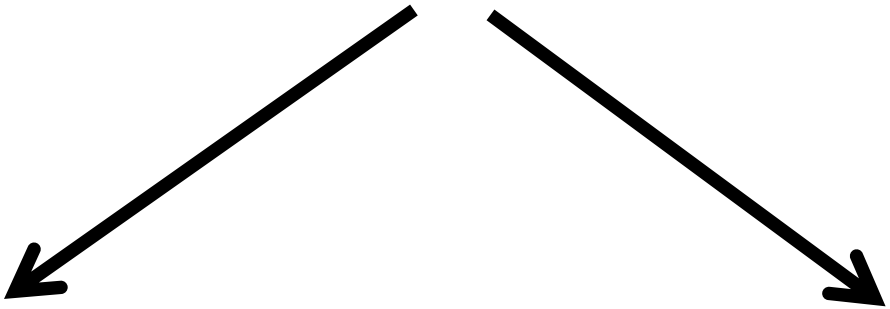
Standard Ibrutinib therapy

Timing	% patients
Resistance before 2 years	6%
Resistance before 5 years	46%
Resistance before 10 years	75%
No resistance after 30 years	5%

Personalized prediction

measure kinetic parameters in individual patient

predict how long ibrutinib monotherapy can maintain control



Long time, e.g. > 10 years
=> therapy ok

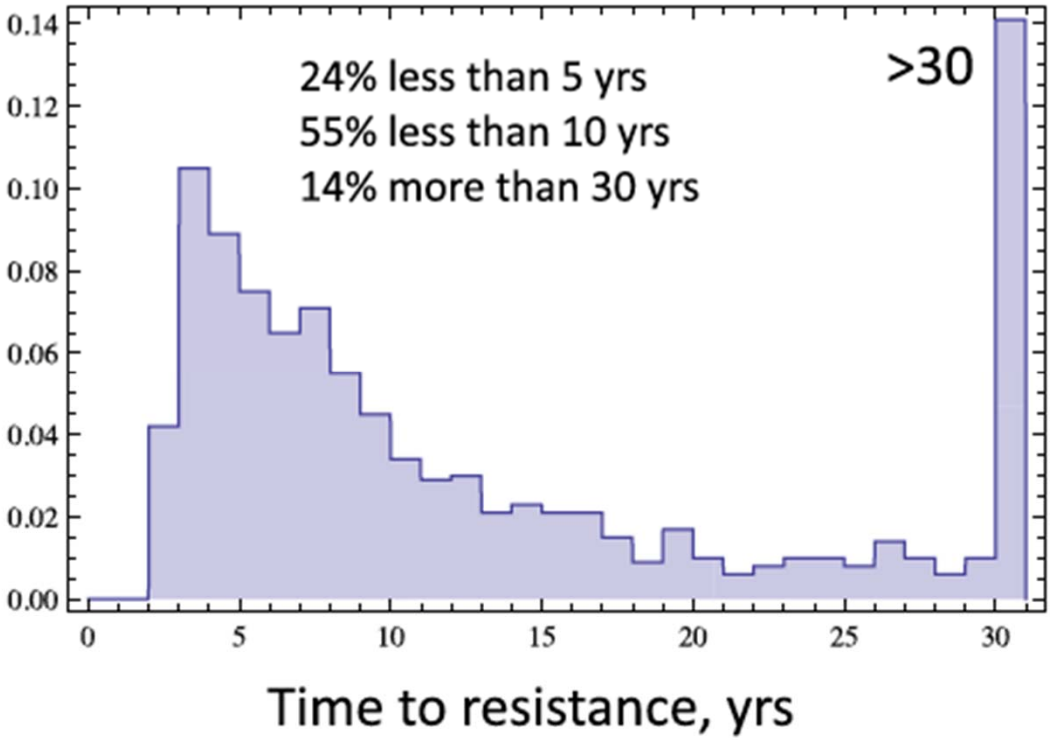
Short time, e.g. 1 year
=> inbrutinib monotherapy is insufficient
=> other approaches neded.

Predictions

Standard Ibrutinib therapy

Timing	% patients
Resistance before 2 years	6%
Resistance before 5 years	46%
Resistance before 10 years	75%
No resistance after 30 years	5%

"Debulking" by a factor of 1/100



Conclusions

- CLL is a disease where all kinetic parameters can be measures in individual patients
- Plugging those into evolutionary models allows us to make personalized predictions about treatment outcomes
- We need to test this predictive ability of the model => work under way in larger patient cohorts and in mice.

Acknowledgements

Mathematical modeling:
Ignacio Rodrigues-Brenes (UCI)
Natalia Komarova (UCI)

Radiology
Naveen Garg (MD Anderson)

Patient data (MD Anderson)
Ohad Benjamini
Michael Keating
William Wiedera
Hagop Kantarjian
Susan O'Brian
Jan Burger

Pharmacyclics
Danelle James