Prostate cancer immunotherapy model

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Presented results were obtained in cooperation with

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- Natalie Kronik, Yuri Kogan, Moran Elishmereni, Karin Halevi- Tobias, Stanimir Vuk-Pavlovic, Zvia Agur,
  "Predicting Outcomes of Prostate Cancer Immunotherapy by Personalized Mathematical Models", PLoS ONE 5(12), 2010: e15482.
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Prostate cancer (PCa) is one of the most common malignancy in men.

Primary treatment includes prostatectomy and/or radiation therapy.

If circulating levels of prostate-specific antigen (PSA) increase after primary therapy, they indicate activation of residual cancer that is then therapeutically controlled by androgen deprivation.

However, disseminated cancer cells often become androgen- independent, leading to another increase in circulating PSA levels and manifesting metastases.

PCa immunotherapy has begun to yield encouraging clinical effects, though not a definitive cure.

The model was built to reflect phase 2 clinical study for an allogeneic PCa whole-cell vaccine which stimulated expansion of tumor-specific immune cells in non-metastatic androgen-independent PCa patients.

The treatment was safe, and the rate of PSA increase (”PSA velocity”) was reduced in 11 out of the 26 studied patients.

Mathematical model describes the basic interactions of a vaccine, immune system and PCa cells.

It was fitted the results of this clinical trial testing an allogeneic PCa whole-cell vaccine.

For model validation the clinically measured changes in prostate- specific antigen (PSA) levels as a correlate of tumour burden was used.

The training set, used for model personalisation, contained the patientñs initial sequence of PSA levels.

The validation set contained his subsequent PSA data points.

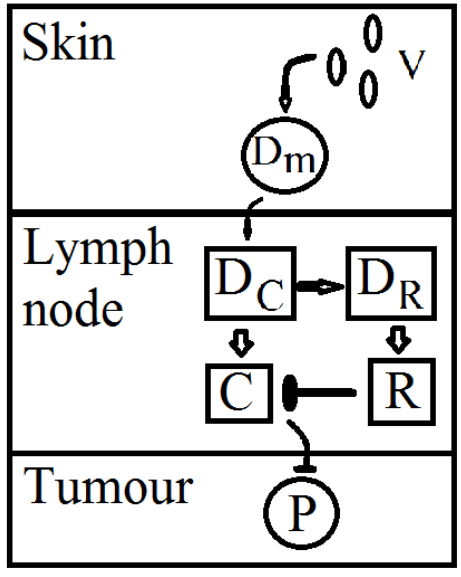
Personalised models were simulated to predict changes in tumour burden and PSA levels and predictions were compared to the validation set.

The model accurately predicted PSA levels over the entire measured period in 12 of the 15 vaccination-responsive patients.

The model describes interactions between:

- $V(t)$ – cellular vaccine,
- $P(t)$ – prostate cancer cells,
- D_m – antigen presenting dermal dendritic cells,
- D_C – mature dendritic cells,

- D_R – "exhausted" dendritic cells,
- R – regulatory/inhibitory cells,
- C – antigen specific effector cells, e.g., cytotoxic T cells.



Scheme of PCa immunotherapy

The model reflects a cascade of immune reactions that can lead to the inhibition of cancer cells invasion.

This cascade is described by the set of ODEs

$$\begin{aligned}
\dot{V} &= -k_l n_V V, \\
\dot{D}_m &= k_l(V + V_p) - k_m D_m, \\
\dot{D}_C &= \alpha_l k_m D_m - k_{CR} D_C, \\
\dot{D}_R &= k_{CR} D_C - \mu_D D_R, \\
\dot{C} &= a_C D_C - \mu_C C - k_R C R, \\
\dot{R} &= a_R D_R - \mu_R R, \\
\dot{P} &= rP - a_P \frac{h_p C P}{h_P + P},
\end{aligned} \tag{1}$$

with initial data reflecting one boost applied to an organism without immunity, that is

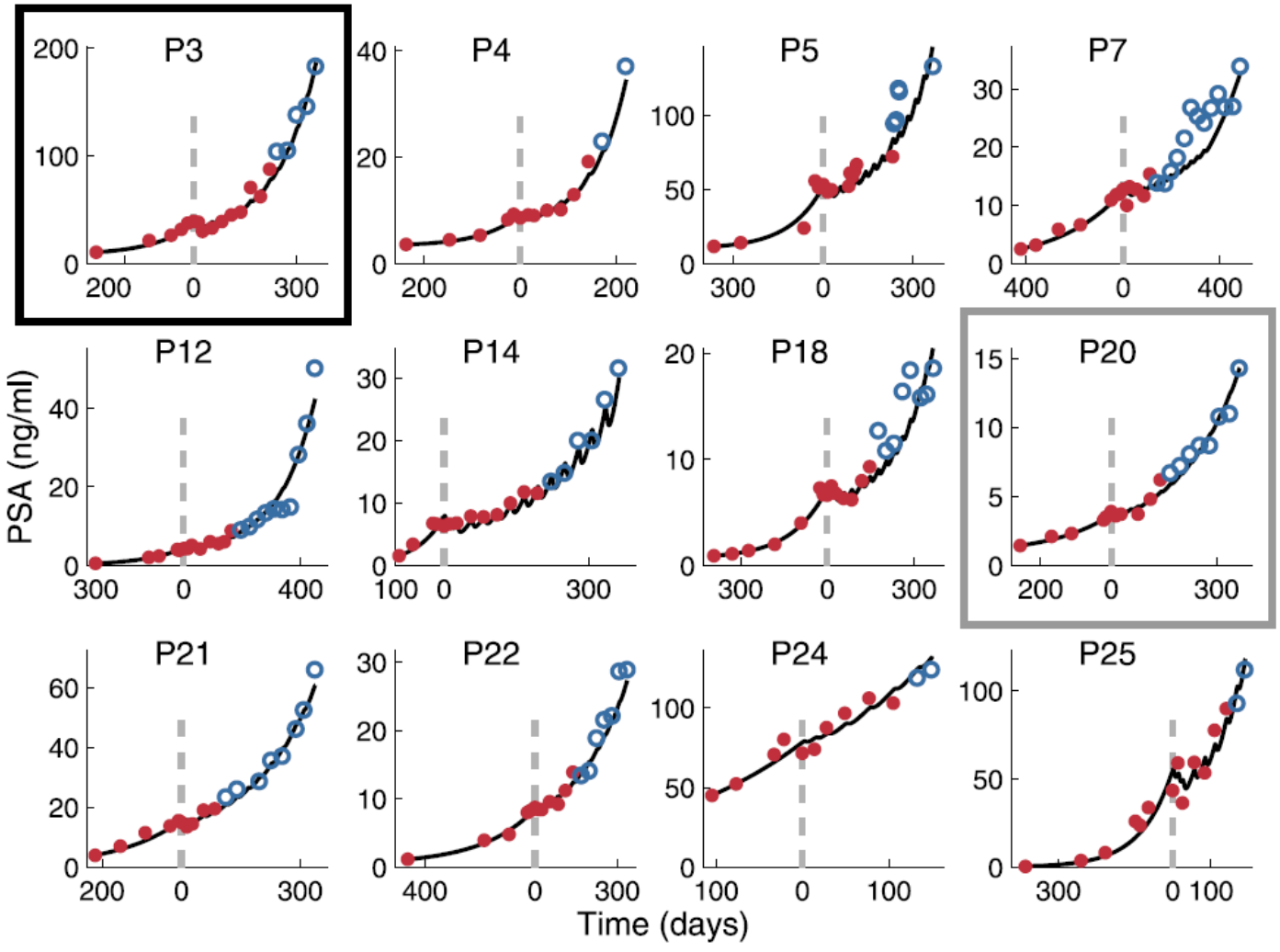
$$(V_0, 0, 0, 0, 0, 0, P_0), \quad V_0,\ P_0 > 0,$$

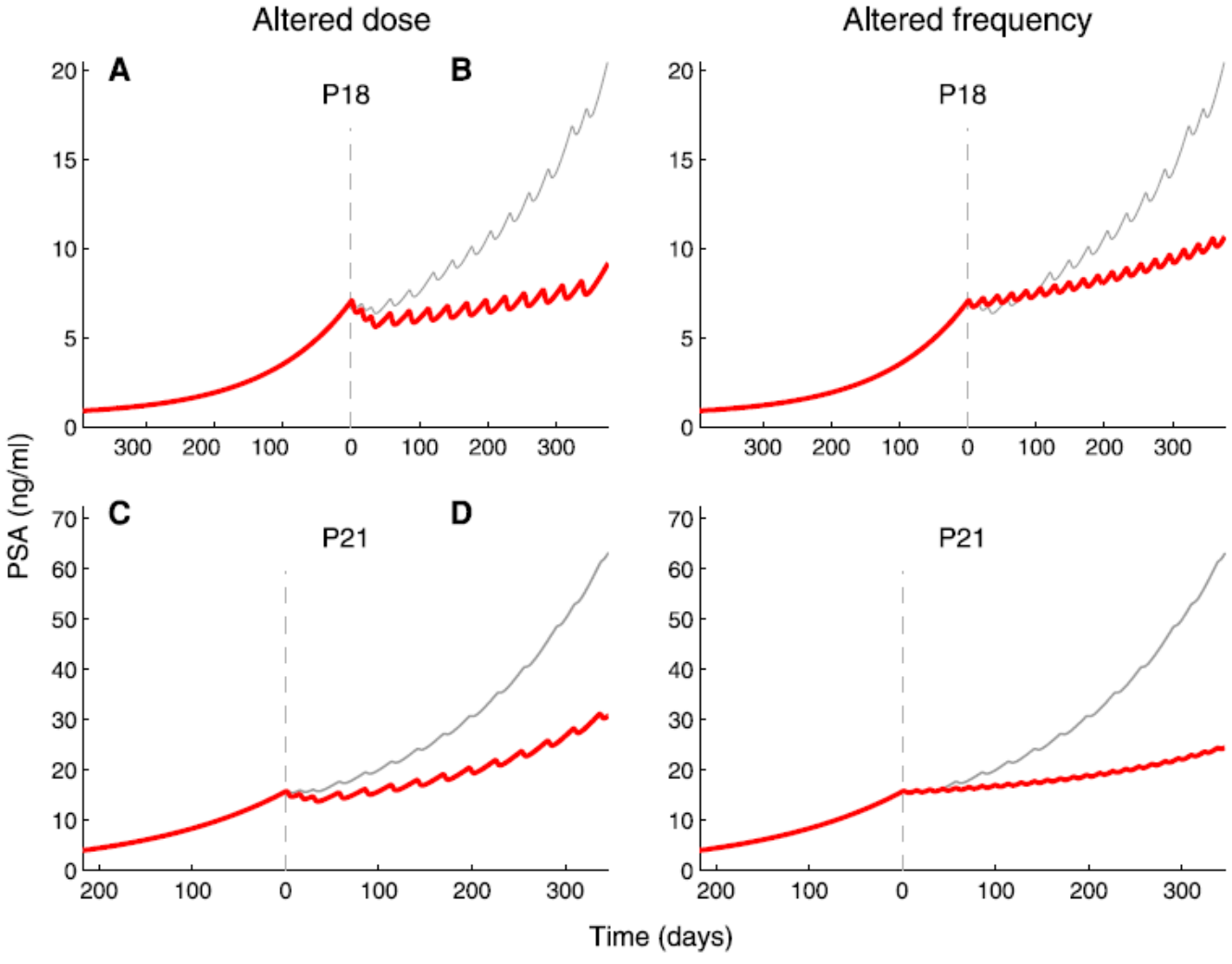
and parameters estimated on the basis of the literature, except some specific parameters:

- k_l – rate of DC maturation following vaccine uptake, $k_l = 0.06\ \mathrm{h}^{-1}$,

- n_V – number of vaccine cells required to induce maturation of one DC, $n_V = 1$,
- V_p – natural influx of mature DCs, $V_P = 0$ (estimated),
- k_m – rate of DC migration from skin to lymph node, $k_m = 0.027\ \mathrm{h}^{-1}$,
- α_l – fraction of antigen-presenting DCs entering the lymph node, $\alpha_l = 0.03$,
- k_{CR} – rate of exhaustion of mature DCs, $k_{CR} = 0.027\ \mathrm{h}^{-1}$,
- μ_D – death rate of exhausted DCs, $\mu_D = 0.014\ \mathrm{h}^{-1}$,
- a_R – rate of inhibitory cell recruitment by exhausted DCs, $a_R = 0.003\ \mathrm{h}^{-1}$,
- μ_R – death rate of inhibitory cells, $\mu_R = 0.03\ \mathrm{h}^{-1}$,
- a_C – rate of effector cell recruitment by mature DCs, $a_C = 0.38\ \mathrm{h}^{-1}$,
- μ_C – effector cell death rate, $\mu_C = 0.007\ \mathrm{h}^{-1}$,

- k_R – rate of effector cell inactivation by inhibitory cells, $k_R = 6 \cdot 10^{-7}$ cell$^{-1}\times$ h^{-1},
- r – tumor growth rate, patient specific, h^{-1},
- a_p – maximal PCa cell killing efficacy, patient specific, cell$^{-1}\times$ h^{-1},
- h_P – Effector cell efficacy damping coefficient, $h_P = 108$ cells.


P3
P4
P5
P7
P12
P14
P18
P20
P21
P22
P24
P25
PSA (ng/ml)
Time (days)


Altered dose
Altered frequency
A
B
C
D
P18
P18
P21
P21
PSA (ng/ml)
Time (days)

Analysis of model (1)

Studying the dynamics of Eqs. (1) we can integrate subsequent equations one by one obtaining the asymptotic dynamics of cancer cells

$$\dot{P} \approx P\left(r - a_P \frac{h_P C_\infty}{h_P + P}\right), \tag{2}$$

where C_∞ is a limit value of $C(t)$.

Let us consider one-dimensional dynamical system defined by (2).

Non-zero steady state $\bar{P}$ of Eq. (2) satisfies the relation

$$r(h_P + \bar{P}) = a_P h_P C_\infty \Rightarrow \bar{P} = \frac{a_P h_P C_\infty}{r} - h_P,$$

and therefore it is positive if C_∞ is sufficiently large.

The dynamics of Eq. (2) depends on the magnitude of C_∞.

- If C_∞ is small such that Eq. (2) has no positive equilibrium, then $\dot{P}(t) > 0$ for every t, and moreover there exists $\delta > 0$ such that $\dot{P} > \delta P$ implying $P \to \infty$ exponentially.
- If C_∞ is sufficiently large, then there exists the positive equilibrium

$$\bar{P} = \frac{a_P h_P C_\infty}{r} - h_P$$

of Eq. (2) and for $0 < P_0 < \bar{P}$ the solution tends to 0, while for $P_0 > \bar{P}$ the solution tends to ∞.

The condition of existence of the positive equilibrium $\bar{P}$ reads

$$\bar{P} = \frac{a_P h_P C_\infty}{r} - h_P > 0 \Leftrightarrow C_\infty > \frac{r}{a_P}.$$

This condition is equivalent to

$$\alpha_l k_l V_P \left(a_P a_C \mu_D \mu_R - r k_{CR} k_R a_R\right) > r \mu_C \mu_D \mu_R k_{CR}.$$

Corollary 1. *To achieve a cure of the disease one needs*

$$\frac{a_P a_C \mu_D \mu_R}{k_{CR} k_R a_R} > r \quad \text{and} \quad V_P > \frac{r \mu_C \mu_D \mu_R k_{CR}}{\alpha_l k_l \left(a_P a_C \mu_D \mu_R - r k_{CR} k_R a_R\right)}.$$

Corollary 1 means that to achieve the cure after one boost the tumour cannot be highly reproductive and moreover natural influx V_P of mature DCs must be sufficiently large.

Notice, that if $V_p = 0$ we have $C_\infty = 0$ and all solutions of Eq. (2) with positive P_0 tend to ∞.

Corollary 2. *For estimated parameter values the cure cannot be achieved after one boost.*

Impulsive vaccination

As a result of Corollary 2 for $V_p = 0$ we need to focus on the case with more boosts applied.

In the following we assume $V_p = 0$ and consider the sequence of boosts V_0 given each time interval Δt.

We obtain impulsive equation for V which can be solved on each $[n\Delta t, (n+1)\Delta t]$, $n \in \mathbb{N}$, interval.

We easily show that V tends to a periodic function as $t \to \infty$. More precisely,

$$V(t) \to V_0 \frac{\mathrm{e}^{-\alpha\Delta t\left(\frac{t}{\Delta t} - \left[\frac{t}{\Delta t}\right]\right)}}{1 - \mathrm{e}^{-\alpha\Delta t}} =: V^{\infty}(t), \tag{3}$$

where $s - [s]$ is the fractional part of $s = \frac{t}{\Delta t}$.

Let us assume $\Delta t = 1$, for simplicity.

Then, the functions D_m, D_C, D_R, R and C are asymptotically periodic with the period equal to 1.

Eventually, we need to study

$$\dot{x} = x\left(r - \frac{H(t)}{1+x}\right), \; x(t_0) = x_0, \tag{4}$$

where $x = \frac{P}{h_P}$ and $H(t) = a_P C(t)$ is smooth and periodic with period 1, $t_0 \in [0,1)$, $x_0 \geq 0$.

We can show that the dynamics of Eq. (4) depends on an average of H.

Let us define $H_A = \int_0^1 H(s)ds$.

Theorem 3. *If $r > H_A$, then $x \to \infty$ for any $x_0 > 0$. If $r < H_A$, then there exists $x^* > 0$ such that*

- *for* $0 < x_0 < x^*$ *the solution* $x(t) \to 0$ *as* $t \to \infty$;
- *for* $x_0 > x^*$ *the solution* $x(t) \to \infty$ *as* $t \to \infty$;
- *for* $x_0 = x^*$ *the solution is periodic.*

Conditions for cure and unsuccessful treatment

Now, we come back to (3), as we would like to combine the magnitude of one boost V_0 with the frequency of vaccine application.

For every $\varepsilon > 0$ there exists $\bar{t}$ such that for any $t > \bar{t}$ we have

$$V \in \left[V_0 \frac{\mathrm{e}^{-\alpha \Delta t}}{1 - \mathrm{e}^{-\alpha \Delta t}} - \varepsilon, V_0 \frac{1}{1 - \mathrm{e}^{-\alpha \Delta t}} \right] =: [V_{\min}, V_{\max}] .$$

Then, for sufficiently large t we obtain the following inequalities:

$$D_m \in \left[\frac{k_l}{k_m} V_{\min}, \frac{k_l}{k_m} V_{\max}\right] =: \left[D_m^{\min}, D_m^{\max}\right],$$

$$D_C \in \left[\frac{\alpha_l k_l}{k_{CR}} D_m^{\min}, \frac{\alpha_l k_l}{k_{CR}} D_m^{\max}\right] =: \left[D_C^{\min}, D_C^{\max}\right],$$

$$D_R \in \left[\frac{k_{CR}}{\mu_D} D_C^{\min}, \frac{k_{CR}}{\mu_D} D_C^{\max}\right] =: \left[D_R^{\min}, D_R^{\max}\right],$$

$$R \in \left[\frac{a_R}{\mu_R} D_R^{\min}, \frac{a_R}{\mu_R} D_R^{\max}\right] =: \left[R_{\min}, R_{\max}\right].$$

$$C \in \left[\frac{a_C D_C^{\min}}{\mu_C + k_R R_{\max}}, \frac{a_C D_C^{\max}}{\mu_C + k_R R_{\min}}\right] =: \left[C_{\min}, C_{\max}\right].$$

Eventually, P is governed by

$$rP - a_P \frac{h_P C_{\max} P}{h_P + P} \leq \dot{P} \leq rP - a_P \frac{h_P C_{\min} P}{h_P + P},$$

and therefore if $C_{\min} > \frac{r}{a_P}$ and $P < \bar{P}_{\min} = h_P \left(\frac{a_P C_{\min}}{r} - 1 \right)$, then $P \to 0$ yielding the cure of the disease.

As ε is arbitrary, we can take a limit $\varepsilon \to 0$ and calculating $C_{\min}$ we obtain

$$C_{\min} = \frac{a_C \alpha_l k_m \mu_R D_m^{\min}}{k_{CR} \left(\mu_C \mu_R + k_R a_R D_R^{\max} \right)} =$$

$$\frac{a_C \alpha_l \mu_R \mu_D k_l^2 V_{\min}}{k_{CR} \left(k_m \mu_C \mu_R \mu_D + k_R a_R \alpha_l k_l^2 V_{\max} \right)}.$$

Using this formula we can approximate the value V_0 which is sufficient to cure the disease for the fixed interval Δt.

We need

$$\frac{a_C \alpha_l \mu_R \mu_D k_l^2 \frac{V_0 \, \mathrm{e}^{-\alpha \Delta t}}{1-\mathrm{e}^{-\alpha \Delta t}}}{k_{CR}\left(k_m \mu_C \mu_R \mu_D + k_R a_R \alpha_l k_l^2 \frac{V_0}{1-\mathrm{e}^{-\alpha \Delta t}}\right)} > \frac{r}{a_P},$$

yielding

$$r < \frac{a_C \mu_R \mu_D a_P}{k_{CR} k_R a_R} =: r_{\max},$$

is the necessary condition to obtain the cure independently of the type of treatment (one or more boosts).

Corollary 4. *If*

$$r < r_{\max} \quad \textit{and} \quad \mathrm{e}^{-\alpha\Delta t} > \frac{r}{r_{\max}},$$

then

$$V_0 > \frac{r k_m k_{CR} \mu_C \mu_R \mu_D (1 - \mathrm{e}^{-\alpha\Delta t})}{k_l^2 \alpha_l \left(a_C \mu_R \mu_D a_P \, \mathrm{e}^{-\alpha\Delta t} - r k_{CR} k_R a_R\right)}$$

is sufficient to cure the disease for

$$P_0 < \bar{P}_{\min} = h_P \left(\frac{a_P C_{\min}}{r} - 1\right).$$

On the other hand, if $P_0 > \bar{P}_{\max} = h_P \left(\frac{a_P C_{\max}}{r} - 1\right)$ *or* $C_{\max} < \frac{r}{a_P}$, *then* $P(t) \to \infty$ *as* $t \to \infty$.

Thank you for your attention!