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Supplemental Information

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In this supporting information we provide details of calculations for the equations in the main text.

1 Calculation of local relaxation times

We define a function $P_n(t)$ as the probability to reach the state n at time t. The dynamics in the system can be described by a set of master equations:

$$\frac{dP_0(t)}{dt} = k_{off}\sum_{n=1}^{N} P_n(t) - k_{on}P_0(t), \tag{S1}$$

for $n = 0$, and

$$\frac{dP_1(t)}{dt} = k_{on}P_0(t) - (k_p + k_{off})P_1(t), \tag{S2}$$

for $n = 1$, and

$$\frac{dP_n(t)}{dt} = k_pP_{n-1}(t) - (k_p + k_{off})P_n(t), \tag{S3}$$

for $1 < n < N$ and

$$\frac{dP_N(t)}{dt} = k_pP_{N-1}(t) - k_{off}P_N(t), \tag{S4}$$

for $n = N$. We also have the normalization condition,

$$\sum_{n=0}^{N} P_n(t) = 1. \tag{S5}$$

In the Laplace language, these equations can be rewritten as

$$(s + k_p + k_{off})\widetilde{P}_n(s) = k_p\widetilde{P}_{n-1}(s); \tag{S6}$$

$$(s + k_p + k_{off})\widetilde{P}_1(s) = k_{on}\widetilde{P}_0(s); \tag{S7}$$

$$(s + k_{off})\widetilde{P}_N(s) = k_p\widetilde{P}_{N-1}(s); \tag{S8}$$

$$(s+k_{on})\widetilde{P}_0(s) = k_{off}\sum_{n=1}^{N}\widetilde{P}_n(s) + 1. \tag{S9}$$

The normalization equation gives

$$\sum_{n=0}^{N}\widetilde{P}_n(s) = \frac{1}{s}. \tag{S10}$$

Eqs. S6, S7, S8, S9 can be solved, yielding

$$\widetilde{P}_0(s) = \frac{(s+k_{off})}{s(s+k_{on}+k_{off})}, \tag{S11}$$

for $n = 0$; and

$$\widetilde{P}_n(s) = \frac{k_{on}(s+k_{off})k_p^{n-1}}{s(s+k_{on}+k_{off})(s+k_p+k_{off})^n}, \tag{S12}$$

for $0 < n < N$; and

$$\widetilde{P}_N(s) = \frac{k_{on}k_p^{N-1}}{s(s+k_{on}+k_{off})(s+k_p+k_{off})^{N-1}}, \tag{S13}$$

and for $n = N$. The stationary probabilities can be found from Eqns. S2, S3, S4 for large times when the left sides of these equations are equal to zero. We obtain then,

$$P_0 = \frac{k_{off}}{k_{on}+k_{off}}. \tag{S14}$$

For $0 < n < N$ it gives

$$P_n = \frac{k_{on}k_{off}k_p^{n-1}}{(k_{on}+k_{off})(k_p+k_{off})^n}, \tag{S15}$$

and for $n = N$,

$$P_N = \frac{k_{on}k_p^{N-1}}{(k_{on}+k_{off})(k_p+k_{off})^{N-1}}. \tag{S16}$$

Now let us derive the times to reach the stationary states at the site n. We define a relaxation function $R_n(t)$, which is given by

$$R_n(t) = 1 - \frac{P_n(t)}{P_n^{(s)}}, \tag{S17}$$

where $P_n^{(s)}$ is the stationary concentration in the state n. The physical meaning of this function is the relative distance to the stationary state at the state n. For $n > 0$, we have $R_n(t = 0) = 1$, and $R_n(t \to \infty) = 0$. Therefore, it can be shown that the average time to reach the stationary concentration at the state n is equal to $\tau_n = \int_0^\infty R_n(t)dt = \widetilde{R}_n(s = 0)$. Using this expression, we obtain the times to reach the stationary states at the fully modified complex $n = N$,

$$\tau_0 = \frac{1}{k_{on}+k_{off}}; \tag{S18}$$

$$\tau_n = \frac{1}{k_{on}+k_{off}} + \frac{n}{k_p+k_{off}} - \frac{1}{k_{off}}; \tag{S19}$$

and

$$\tau_N = \frac{1}{k_{on} + k_{off}} + \frac{N-1}{k_p + k_{off}}. \tag{S20}$$

Fig. S1 presents our theoretical predictions on the dependence of the relaxation times on the phosphorylation rate k_p, on the complex formation rate k_{on} and on the complex dissociation rate k_{off}. It shows that for experimentally relevant parameters τ_N depends relatively weakly on the association rate, while it is more sensitive to changes in the dissociation and phosphorylation rates. Increasing k_p or k_{off} lowers the relaxation time. The reason for this behavior can be understood from the chemical kinetic scheme. The dominating term in the relaxation time [see Eq. (S20)] is the time to move through the sequence of the phosphorylation events starting from the state $n = 1$ and finishing in the state $n = N$, and it depends only on k_p and k_{off}. For larger k_{on} and k_p, the phosphorylations are fast and this lowers the overall relaxation times, as expected. In addition, increasing k_{off} accelerates the formation of the stationary state between TCR-ligand bound and ligand unbound states.

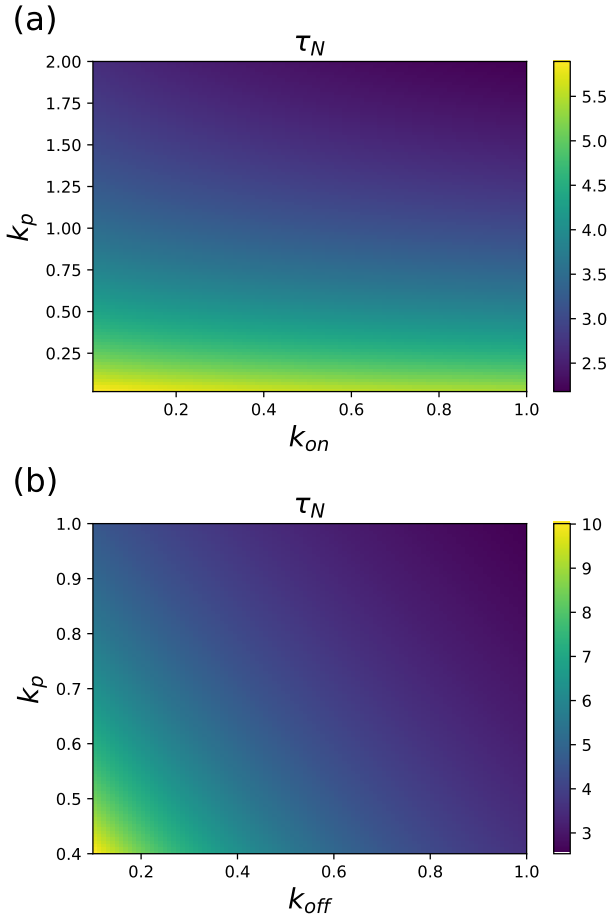

Figure S1: Heat maps for the relaxation times τ_N (in seconds) as a function of the transition rates in the system: (a) varying k_p - k_{on} (in s^{-1}) parameter space (with $k_{off} = 1\ s^{-1}$ and $N = 6$), and (b) varying k_p - k_{off} (s^{-1}) parameter space (with $k_{on} = 1\ s^{-1}$ and $N = 6$).

2 Calculation of mean first-passage times and their variances

In this section, we calculate the mean first passage time to reach a specific state. Since we only consider the first-passage times, the system dynamics become independent of the initial equilibrium binding as shown in Fig S2. Here we present a model with homogeneous kinetic rates. The equations can be easily solved for inhomogeneous rates. We define $F_n(t)$ as the probability to reach state N at time t if at $t = 0$ the system starts in the state $n = 1$. Time evolution of this function is governed by following backward master equation:

$$\frac{dF_n}{dt} = k_p F_{n+1} - (k_{off} + k_p) F_n \tag{S21}$$

with initial condition $F_N(t) = \delta(t)$. After performing Laplace transform we obtain

$$(s + k_p + k_{off})\widetilde{F}_n(s) = k_p \widetilde{F}_{n+1}(s) \tag{S22}$$

This equation leads to a full exact solution,

$$\widetilde{F_1}(s) = \left(\frac{k_p}{s + k_{off} + k_p}\right)^{N-1}. \tag{S23}$$

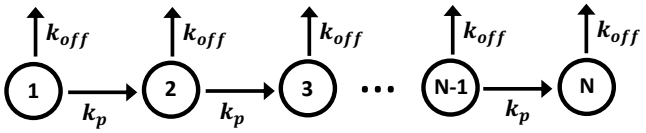

Figure S2: Schematic diagram for calculations of mean-first passage times.

We define T_n as a mean-first passage time to reach the state N from the the state n. Using the probability density function $F_n(t)$, it can be written as

$$< T_1 >= \frac{\int_0^\infty t F_1(t) dt}{\int_0^\infty F_1(t) dt} = \frac{-\frac{\partial \widetilde{F_1}}{\partial s}|_{s=0}}{\widetilde{F_n}(s=0)}. \tag{S24}$$

Thus, the first-passage time is given by

$$< T_1 >= \frac{N-1}{k_{off} + k_p}. \tag{S25}$$

Now we can calculate the second moment for mean-first passage time,

$$< T_1^2 >= \frac{\int_0^\infty t^2 F_1(t) dt}{\int_0^\infty F_1(t) dt} = \frac{-\frac{\partial^2 \widetilde{F_1}}{\partial s^2}|_{s=0}}{\widetilde{F_n}(s=0)}. \tag{S26}$$

which after some algebra leads to

$$< T_1^2 >= \frac{N(N-1)}{(k_{off} + k_p)^2}. \tag{S27}$$

Variance of mean first passage time is given by

$$\sigma T_1 = \sqrt{< T_1^2 > - < T_1 >^2} = \frac{\sqrt{N-1}}{k_{off} + k_p} \tag{S28}$$

TCR	IA^b+3K mutation	K_D (μM)	k_{on} ($M^{-1}s^{-1}$)	k_{off} (1/s)	$t_{1/2}$ (s)	Proliferation EC_{50} (nM)	TNF-α EC_{50} (nM)
B3K506	WT	7	101918	0.7	0.9	0.2	3.1
B3K506	P5R	11	74654	0.8	0.9	0.2	6.0
B3K506	P8R	13	64318	0.8	0.8	0.3	7.0
B3K506	P-1A	26	101731	2.6	0.3	9.0	68.0
B3K506	P8A	92	33370	3.1	0.2	1200.0	2210.0
B3K506	P-1K	101	55149	5.6	0.1	660.0	5500.0
B3K508	WT	29	10887	0.3	2.2	0.4	6.0
B3K508	P5R	93	11048	1.0	0.7	15.0	87.0
B3K508	P2A	175	19914	3.5	0.2	71.0	530.0

Table 1: The data and kinetic parameters are taken from Ref. 7 in the main text.

peptide name	peptide sequence	k_{off} (1/s)	$k_{on}\times10^{-3}$ ($M^{-1}\ s^{-1}$)	$EC_{50}(IFN-\gamma)$ (μg/ml pMHC)	predicted activity
ESO-9C	SLLMWITQC	0.82 ±0.01	57 ±3	115 ±14	foreign
ESO-9L	SLLMWITQL	0.93 ±0.05	17 ±2	42 ±113	self
ESO-9V	SLLMWITQ V	0.33 ±0.01	45 ±4	180 ±19	foreign
ESO-3A	SLAMWITQV	0.31 ±0.01	47 ±4	70 ±15	foreign
ESO-3I	SLIMWITQV	0.61 ±0.04	35 ±3	94 ±16	foreign
ESO-3M	SLMMWITQV	0.38 ±0.01	42 ±1	48 ±7	foreign
ESO-3Y	SLYMWITQV	1.15 ±0.04	38 ±1	240 ±50	self
ESO-4D	SLLDWITQV	2.59 ±0.15	10 ±1	661 ±85	self
ESO-6V	SLLMWVTQV	0.85 ±0.03	49 ±2	45 ±5	foreign
ESO-6T	SLLMWTTQV	1.30 ±0.03	13 ±1	228 ±62	self
ESO-7H	SLLMWIHQV	1.73 ±0.09	17 ±2	526 ±201	self
A2-R65	SLLMWITQV	1.93 ±0.13	17 ±1	479 ±12	self
A2-H70	SLLMWITQV	0.22 ±0.01	2.7 ±0.1	151 ±19	foreign
A2-H74	SLLMWITQV	0.49 ±0.01	19 ±1	107 ±12	foreign
A2-R75	SLLMWITQV	0.39 ±0.00	23 ±1	99 ±12	foreign
A2-V76	SLLMWITQV	0.67 ± 0.01	31 ± 2	146 ± 38	foreign
A2-K146	SLLMWITQV	0.48 ± 0.01	24 ± 2	179 ± 23	foreign

Table 2: Kinetic parameters and activation potency 1G4 TCR interaction with pMHC variants. (table adapted from Ref. 31 in the main text).