Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Tun KM, Imwong M, Lwin KM, et al. Spread of artemisinin-resistant Plasmodium falciparum in Myanmar: a cross-sectional survey of the K13 molecular marker. Lancet Infect Dis 2015; published online Feb 20. http://dx.doi.org/10.1016/S1473-3099(15)70032-0.
Supplementary Information

Model-based Method
A Bayesian geostatistical model of the proportion of individuals with any marker (>440 amino acids into the protein) was developed. The number of individuals in each study with a resistance mutation ($N_i^+$) was assumed to be binomially distributed, given the number of individuals in the study ($N_i$) and the probability $P(x_i)$:

$$N_i^+ | N_i, P(x_i) \sim \text{Binomial}(N_i, P(x_i)).$$

The probability, $P(x)$, at an arbitrary location $x$, was modelled as the inverse logit transformation of the sum of a random field, $f(x)$, and an unstructured random component, $\varepsilon(x)$:

$$P(x) = \text{logit}^{-1}(f(x) + \varepsilon(x)).$$

The unstructured components, $\varepsilon(x)$, were assumed to be independent and identically distributed with zero mean and variance $V$ while the random field, $f(x)$, was modelled as a stationary Gaussian process, with constant mean function $\mu_0$ and Matern covariance function, $C(x)$

$$f(x) | \mu_0, \sigma, \nu, \kappa \sim \text{GP}(\mu_0, C(x))$$

where $\mu_0$ is the mean parameter, $\sigma$ is the spatial scale parameter, $\kappa$ is the partial sill and $\nu$ is the degree of differentiability parameter. The covariance between a study conducted at location $x_i$ and a study performed at $x_j$ was given by

$$C(x_i, x_j) = \frac{2}{\kappa^2} G(\sigma^2, \nu, \kappa^2, \nu, \kappa^2, \nu, \kappa^2, \nu, \kappa^2),$$

where $D_{GC}(x_i, x_j)$ is the great circle distance, $G$ is the gamma function and $K_\nu^\kappa$ is the modified Bessel function of the second kind of order $\nu$. The following priors were imposed:

$$p(\mu_0) \sim \text{Exponential}(1)$$
$$x \sim \text{Uniform}(0, 3)$$
$$V \sim \text{Exponential}(0.1)$$
$$s \sim \text{Exponential}(0.1)$$

Using the Python module PyMC, the model was fitted with Markov chain Monte Carlo (MCMC) [1,2]. Predictive maps were generated on a 5 x 5 km grid from the MCMC samples. For each prediction location, prevalences were drawn and the distribution summarized with the median and standard deviation of this set.

1. Patil A, Huard D, Fonnesbeck C (2010) PyMC: Bayesian Stochastic Modelling in Python. Journal of Statistical Software 35: 1-81.
2. Patil A (2010) PyMC Gaussian process module Users guide.
**Kriging Method**

Let \( z(x_k), \ k = 1, 2 \ldots n \) be the observed values of the variable \( z \) at locations \( x_1, x_2, \ldots x_n \)

We require to find coefficients \( \lambda_k \) for \( k = 1, 2, \ldots n \), such that the estimate \( \hat{z}_0 \) of \( z_0 (=z(x_0)) \) at any point \( x_0 \)

\[
\hat{z}_0 = \sum_{k=1}^{n} \lambda_k z(x_k)
\]

(1)

minimize the mean squared prediction error (referred to as ‘the kriging variance’)

\[
\sigma_e^2 = E[(z_0 - \hat{z}_0)^2]
\]

(2)

subject to the constraint (to ensure unbiased)

\[
1 = \sum_{k=1}^{n} \lambda_k
\]

(3)

2.1 Kriging coefficients \( w_k \)

Denoting \( z_0 \) as a random variable and recalling that in ordinary kriging \( E[z_0] = \mu \) where \( \mu \) is an unknown but constant mean, we first note that

\[
\sigma_e^2 = E[(z_0 - \hat{z}_0)^2] = \text{Var}(z_0 - \hat{z}_0) + E[(z_0 - \hat{z}_0)^2]
\]

and because by unbiasedness \( E[(z_0 - \hat{z}_0)^2] = 0 \),

\[
= \text{Var}(z_0) + \text{Var}(\hat{z}_0) - 2\text{Cov}(\hat{z}_0, z_0)
\]

(4)

Using the method of Lagrange multipliers we therefore require to minimize the Lagrangian

\[
L = \text{Var}(z_0 - \hat{z}_0) + 2\beta \left( \sum_{k=1}^{n} \lambda_k - 1 \right)
\]

where \( \sigma^2 \) is the variance of \( z_0 \) and \( \text{Cov}(x,y) \) is the covariance of \( x \) and \( y \). This is achieved by taking partial derivatives of \( L \) with respect to \( \lambda_k \) for \( k = 1, 2, \ldots n \) and the \( \beta \) and then setting each to zero, which yields a homogeneous system of \( n \) simultaneous equations which can be written in matrix form as
The kriging coefficients $\lambda_k$ and the Lagrange multiplier $\beta$ are then found by multiplying the right hand side vector in equation (8) by the inverse matrix $C^{-1}D$

\[ \lambda = C^{-1}D \]  \tag{6}

2.1 Kriging coefficients $\lambda_k$ in terms of the variogram

The variogram can be written in terms of the covariance function as

\[ \gamma_{ij} = \frac{1}{2} \text{Var}(z(x_i) - z(x_j)) = \frac{1}{2} \left( \sigma^2 + \sigma^2 - 2\text{Cov}(z(x_i) - z(x_j)) \right) = \sigma^2 - \text{Cov}(z(x_i) - z(x_j)) \]

So we have that

\[ \text{Cov}(z(x_i) - z(x_j)) = \sigma^2 - \gamma_{ij} \]

and the kriging equations (5) can be rewritten equivalently in terms of the variogram as

\[ \begin{bmatrix} -\gamma_{11} & \cdots & -\gamma_{1n} & 1 \\ \vdots & \ddots & \vdots & \vdots \\ -\gamma_{n1} & \cdots & -\gamma_{nn} & 1 \\ 1 & \cdots & 1 & 0 \end{bmatrix} \begin{bmatrix} \lambda_1 \\ \vdots \\ \lambda_n \\ \beta \end{bmatrix} = \begin{bmatrix} -\gamma_{10} \\ \vdots \\ -\gamma_{n0} \\ 1 \end{bmatrix} \]  \tag{7}

or more compactly

\[ \Gamma \lambda = \Gamma_0 \]  \tag{8}

Kriging coefficients $\lambda_k$ and the Lagrange multiplier $\beta$ are found multiplying the right hand side by the inverse matrix $\Gamma^{-1}$

\[ \lambda = \Gamma^{-1} \Gamma_0 \]
2.3 Kriging variance $\sigma^e_2$

Multiplying $i$th row of matrix $C$ and $D$ in equation (5) by $\lambda_i$ for $i = 1 \ldots n$ and forming their sum gives

$$\sum_{i=1}^{n} \lambda_i \sum_{j=1}^{n} \lambda_j \text{Cov}(z(x_i), z(x_j)) + \sum_{i=1}^{n} \lambda_i \beta = \sum_{i=1}^{n} \lambda_i \text{Cov}(z(x_i), z_0)$$

From equation (4) the kriging variance is then given by

$$\sigma^e_2 = \sigma^2 + \sum_{k=1}^{n} \sum_{j=1}^{n} \lambda_k \lambda_j \text{Cov}(z(x_k), z(x_j)) - 2 \left( \sum_{k=1}^{n} \lambda_k \text{Cov}(z(x_k), z_0) \right)$$

$$= \sigma^2 + \sum_{i=1}^{n} \lambda_i \text{Cov}(z(x_i), z_0) - \beta$$

$$= \sigma^2 - \lambda^T \mathbf{D}$$

(9)

where $\lambda^T$ denotes the transpose of vector $\lambda$ from equation (6).

2.4 Kriging variance $\sigma^e_2$ in terms of the variogram

The kriging variance $\sigma^e_2$ can similarly be expressed in terms of the variogram by replacing covariance terms in vector $\mathbf{D}$ of equation (8)

$$\mathbf{D} = \begin{bmatrix} \text{Cov}(z(x_1), z_0) \\ \vdots \\ \text{Cov}(z(x_n), z_0) \\ 1 \end{bmatrix} = \begin{bmatrix} \sigma^2 - \gamma_{10} \\ \vdots \\ \sigma^2 - \gamma_{n0} \\ 1 \end{bmatrix}$$

so that from equation (9)

$$\sigma^e_2 = \sigma^2 - \lambda^T \mathbf{D}$$

$$= \sigma^2 - [\lambda_1 \ldots \lambda_n | \beta] \begin{bmatrix} \sigma^2 - \gamma_{10} \\ \vdots \\ \sigma^2 - \gamma_{n0} \\ 1 \end{bmatrix}$$

$$= \sigma^2 - \sigma^2 \sum_{i=1}^{n} \lambda_i - \sum_{i=1}^{n} \lambda_i \gamma_{i0} + \beta$$

$$= \sum_{i=1}^{n} \lambda_i \gamma_{i0} - \beta$$
## Supplementary Table

List of mutations found in 940 samples

| Mutation | Number of samples with mutation | Number of States/Regions where mutation was found | Notes and references |
|----------|---------------------------------|---------------------------------------------------|----------------------|
| **Unique to this survey** | | | |
| N371I | 1 | 1 | |
| P443S | 4 | 2 | |
| N458I | 9 | 1 | |
| S485N | 1 | 1 | |
| N490T | 1 | 1 | |
| P527H | 1 | 1 | |
| G533A | 3 | 2 | |
| A675V | 5 | 2 | |
| A676D | 6 | 3 | |
| **Previously reported in Myanmar or Myanmar-Thailand border** $^5, 18, 36$ | | | |
| E252Q | 17 | 3 | |
| K438N | 1 | 1 | |
| P441L | 8 | 2 | |
| F446I | 80 | 6 | |
| G449A | 5 | 4 | Also reported in Cambodia$^4$ |
| D452E | 1 | 1 | |
| N458Y | 2 | 1 | Also reported in Cambodia$^{4, 5}$ |
| C469F | 1 | 1 | |
| M476I | 18 | 2 | |
| K479I | 8 | 1 | |
| A481V | 1 | 1 | Also reported in Cambodia$^4$ |
| N537I | 15 | 2 | Also reported in Cambodia$^4$ |
| G538V | 30 | 3 | |
| R561H | 25 | 5 | Also reported in Cambodia$^4$ |
| P574L | 41 | 7 | Also reported in Cambodia$^4$ |
| R575K | 6 | 2 | |
| C580Y | 97 | 2 | Also reported in Cambodia$^{4, 5}$ |
| F614L | 1 | 1 | |
| **Previously reported in Cambodia only**$^6$ | | | |
| H719N | 2 | 1 | |
| **Previously reported in Africa only**$^5$ | | | |
| R255K | 2 | 2 | |
Supplementary Figure 1

Variogram produced by the kriging approach. An empirical variogram was constructed as a scatter plot (squares) of semivariance $\gamma(h)$ versus lag distance $h$ to describe spatial dependence in the data collected. The plot describes how variation in estimated K13 mutation prevalence observed between different sample sites is dependent on (Euclidean) separation distance between those sites. The plot was constructed by binning all pairwise site distances into a default 20 bins, each at a fixed increment apart. Spatial dependence can be seen to decrease as the distance between the sample data sites is increased. Such a plot will typically achieve a plateau (referred to as a 'sill') after a certain separation distance (referred to as the 'range') exhibited by a 'flattening of the curve' as is illustrated in the plot after a lag distance of approximately 4 separation units (20 km).