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An adaptive design for the identification of the optimal dose using joint modeling of continuous repeated biomarker measurements and time-to-toxicity in phase I/II clinical trials in oncology

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Abstract

We present a new adaptive dose-finding method, based on a joint modeling of longitudinal continuous biomarker activity measurements and time to first dose limiting toxicity (DLT), with a shared random effect. Estimation relies on likelihood that does not require approximation, an important property in the context of small sample sizes, typical of phase I/II trials. We address the important case of missing at random data that stem from unacceptable toxicity, lack of activity and rapid deterioration of phase I patients. The objective is to determine the lowest dose within a range of highly active doses, under the constraint of not exceeding the maximum tolerated dose (MTD). The MTD is associated to some cumulative risk of DLT over a predefined number of treatment cycles. Operating characteristics are explored via simulations in various scenarios.

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Keywords
Cumulative toxicity, Dose-finding, Joint modeling, Likelihood inference, Longitudinal measurements

1 Appendix

In this Appendix readers can find additional information regarding our simulation studies and the sensitivity analysis. More precisely, 1 figure and 9 tables are presented.

Table 1 presents the bias and covarage results of the joint model under six different sample sizes. Biomarker measurements of the longitudinal model were assumed to be unbalanced.

Table 2 presents the Pocock-type boundary that was used to implement the stopping rule. The stopping rule is applied on the first 15 patients and (b_N) shows how many of them should experience a DLT before stopping the trial due to excessive toxicity.

Table 3 presents the values that were used to generate both survival and longitudinal data for the eight principal scenarios that are presented in table 2 of the article.

Tables 4 to 11 present the results of the sensitivity analysis. More precisely, scenarios investigated in table 4 and table 5 are identical to the principal scenarios that are presented in table 2 of the article. The purpose was to examine the model robustness under larger variances, smaller sample sizes and misspecification of the random effect distribution. For table 4 we assumed larger variances than the ones of table 2 of the article. In table 5 the first seven scenarios were evaluated under both larger variances and a smaller sample size. The seven scenarios at the end of the table were generated assuming that the random effect distribution between the survival and the longitudinal model was not the same. For the linear mixed effects model we assumed that the random effects follow a Gamma distribution whereas for the probit model the standard normal distribution. The case where all doses are extremely toxic was not investigated in the sensitivity analysis.

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In tables 6 and 7 activity data was generated from misspecified longitudinal models. For scenarios of table 6, biomarker data was generated assuming that we have both a random intercept and a random slope; σ_3 being the standard deviation of the random intercept and ρ_{σ_1,σ_3} the correlation between the two random effects. For the survival model nothing was modified. In table 7 we assumed a linear mixed effects model that included both a linear and a quadratic term for time,

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij} d_i + \beta_4 t_{ij} log(\sqrt{d_i} + 1) + u_i t_{ij} + r_{ij}.$$

Again the survival model was not modified.

As part of our sensitivity analysis, we have simulated a different biomarker-time relationship that corresponds to that depicted in figure 1. This trajectory refers to biomarkers, discussed in the article, that reflect the direct action of the treatment such as the plasma concentration or the level of antibodies binding to their target. When patients respond to the treatment the levels of the biomarker increase with time and when they progress the levels decrease. We have explored our design under these types of biomarkers by simulating two additional scenarios (table 8). Data for the biomarker was generated from the same linear mixed effects model we have used throughout the article,

$$y_{ij} = \beta_0 + \beta_1 t_{ij}^2 + \beta_2 t_{ij} d_i + \beta_3 t_{ij} log(\sqrt{d_i} + 1) + u_i t_{ij} + r_{ij}.$$

The difference when generating patient data for the CA 125 and the above biomarkers was related to the model parameters. More specifically, for parameters β_1, β_2, and β_3 the signs were inverted. So β_1 was negative, β_2 positive, and β_3 also positive. Scenarios 8.1 and 8.2 were generated in a such a way to match scenarios 5 and 2, respectively, from table 3 of the article, at least in terms of toxicity and OD. Patients were censored due to lack of activity when their biomarker measurements decreased by more than 20 units/ml, after reaching the maximum activity. The percentage of correct OD selection was the same for scenarios 8.1 and 5 and differed by 6% for 8.2 and 2. Thus, we conclude that there are no substantial differences stemming from the pattern of the biomarker over time.

Table 9 presents results from additional sensitivity analysis that are not discussed in the article. We investigated how the design performs under model misspecification. The goal was to examine which of the two models, longitudinal or survival, has a greater impact on the results when not correctly specified. To that end, for scenarios 9.1 to 9.3 activity data was generated from a saturated mixed effects model with a

separate parameter for every dose level, whereas nothing changed for toxicity data. On the contrary, for scenarios 9.4 to 9.6 toxicity data was generated from a logistic model and activity data from the same linear mixed effects model we use throughout the study. The percentage of correct OD identification was not highly modified. The impact of model misspecification was comparable, irrespectively of which model was misspecified.

Table 10 shows 2 scenarios with a modified definition of "equally" active doses and finally, table 11 depicts the results after modifying 2 of the 3 criteria for joint modeling implementation.

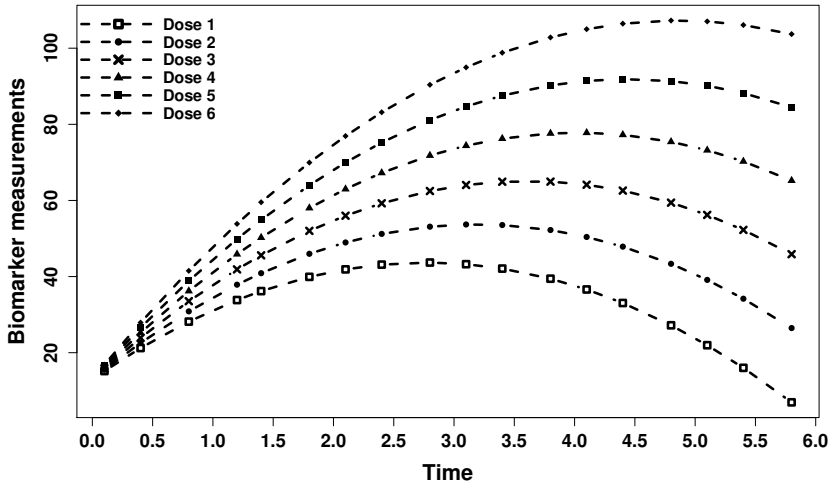

Figure 1. Biomarker trajectory over time and for 6 dose levels.

Table 1. Simulation results of 2000 replicates. Shown are the percentage of bias and the coverage of the joint model parameters over six different sample sizes: $N = 15$, $N = 20$, $N = 25$, $N = 30$, $N = 40$, and $N = 60$ and for unbalanced data for the linear mixed effects model.

Parameter	Bias						Coverage					
	N=15	N=20	N=25	N=30	N=40	N=60	N=15	N=20	N=25	N=30	N=40	N=60
Longitudinal												
β_0	-1.18	-0.36	-0.16	-0.10	-0.13	-0.02	0.92	0.93	0.95	0.95	0.95	0.94
β_1	-0.18	0.02	0.00	0.00	-0.01	-0.01	0.91	0.93	0.94	0.93	0.94	0.95
β_2	0.58	-0.13	0.20	0.02	0.02	-0.08	0.89	0.91	0.91	0.92	0.93	0.94
β_3	-14.92	4.00	5.40	-0.25	-0.13	2.30	0.92	0.90	0.91	0.93	0.93	0.93
σ_1	-5.32	-8.20	-8.30	-7.30	-5.90	-6.20	0.90	0.99	0.99	0.99	0.99	0.98
σ_2	12.00	-3.40	-2.50	-2.10	-1.40	-0.88	0.98	0.97	0.97	0.97	0.96	0.96
Survival												
a_0	1.28	0.23	-0.19	0.15	-0.12	0.09	0.98	0.97	0.95	0.95	0.95	0.95
a_1	-27.42	13.50	8.80	7.50	6.01	3.10	0.98	0.97	0.97	0.96	0.96	0.95
γ	368.71	40.62	-25.37	12.29	10.96	-2.70	0.99	0.99	0.99	0.99	0.99	0.97

Table 2. Pocock-type sequential boundaries to monitor dose-limiting toxicity rate, during the first treatment cycle. Toxicity rate was set at 35% and the one-sided level test at 10%.

Number of patients, (N)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, (b_N)	-	-	3	4	4	5	5	5	6	6	7	7	8	8	8

Table 3. Joint model parameters for data generation of the eight principal scenarios. Standard deviations were fixed at $\sigma_1 = 1$ and $\sigma_2 = 3$, and the parameter of the shared random effect at $\gamma = 0.1$.

Parameter	Scenario							
	1	2	3	4	5	6	7	8
Longitudinal								
β_0	270	90	115	115	80	270	115	90
β_1	35	8.5	15	15	7	35	10	8.5
β_2	-80	-19	-31.5	-31.5	-11	-80	-27	-19
β_3	-4	-4	-4	-4	-4	-4	-4	-4
Survival								
a_0	7.50	7.43	5.20	7.43	5.82	7.20	7.20	2.70
a_1	0.33	0.33	0.30	0.33	1.94	0.30	0.30	1.50
a_g	-3.30	-3.30	-3.50	-3.30	-3.12	-2.90	-2.90	-2.60

Table 4. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). The simulated scenarios are the same as in table 2 of the article. Residual standard deviation was $\sigma_2 = 4$ and random effect standard deviation $\sigma_1 = 2$. The optimal dose is in bold and the MTD in italic.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
1	$(Y_{(l),min}, p_l)$	(200, 0.00)	(176, 0.00)	(147, 0.02)	(115, 0.12)	***(79, 0.38)***	(40, 0.75)	
	$P_{\%}$	0.0	0.0	0.0	1.0	97.8	1.2	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.2	5.4	40.7	7.7	
2	$(Y_{(l),min}, p_l)$	(71, 0.00)	(64, 0.00)	**(57, 0.03)**	(49, 0.12)	*(39, 0.38)*	(29, 0.75)	
	$P_{\%}$	0.3	10.7	80.0	8.5	0.5	0.0	0.0
	$\bar{N}_{pat}$	2.3	7.2	31.4	8.2	5.8	5.1	
3	$(Y_{(l),min}, p_l)$	***(87, 0.32)***	(78, 0.71)	(67, 0.96)	(55, 0.99)	(41, 0.99)	(26, 0.99)	
	$P_{\%}$	99.4	0.2	0.0	0.0	0.0	0.0	0.4
	$\bar{N}_{pat}$	51.6	6.3	2.0	0.1	0.0	0.0	
4	$(Y_{(l),min}, p_l)$	(87, 0.00)	(78, 0.00)	(67, 0.03)	**(55, 0.12)**	*(41, 0.38)*	(26, 0.75)	
	$P_{\%}$	0.1	0.0	3.9	91.5	4.5	0.0	0.0
	$\bar{N}_{pat}$	2.0	2.1	5.5	36.3	9.0	5.0	
5	$(Y_{(l),min}, p_l)$	**(71, 0.02)**	(68, 0.07)	(65, 0.20)	*(61, 0.43)*	(57, 0.68)	(52, 0.88)	
	$P_{\%}$	99.6	0.2	0.0	0.2	0.0	0.0	0.0
	$\bar{N}_{pat}$	29.4	3.6	6.3	11.5	7.8	1.4	
6	$(Y_{(l),min}, p_l)$	(200, 0.00)	(176, 0.00)	(147, 0.01)	(115, 0.04)	(79, 0.16)	***(40, 0.41)***	
	$P_{\%}$	0.2	0.0	0.0	0.0	5.3	94.5	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.0	2.4	8.1	43.4	
7	$(Y_{(l),min}, p_l)$	(84, 0.00)	(73, 0.00)	(61, 0.01)	(48, 0.04)	**(32, 0.16)**	*(16, 0.41)*	
	$P_{\%}$	0.0	0.0	0.0	14.9	84.9	0.2	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.2	9.3	34.2	10.3	

Table 5. Sensitivity analyses of 2000 replicates. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$), under the scenarios of table 4, with different standard deviations, sample size, and random effects' distributions.

Conditions	Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
N=40									
$\sigma_1 = 2$ and $\sigma_2 = 4$									
	1	$P_{\%}$	0.0	0.0	0.0	3.6	90.8	5.6	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.2	5.1	21.7	7.0	
	2	$P_{\%}$	0.4	11.9	74.4	11.9	1.4	0.0	0.0
		$\bar{N}_{pat}$	2.2	4.8	16.0	6.6	5.5	4.9	
	3	$P_{\%}$	99.5	0.2	0.0	0.0	0.0	0.0	0.3
		$\bar{N}_{pat}$	31.9	6.0	1.9	0.2	0.0	0.0	
	4	$P_{\%}$	0.0	0.0	6.9	83.1	10.0	0.0	0.0
		$\bar{N}_{pat}$	2.0	2.1	4.6	18.6	7.8	4.9	
	5	$P_{\%}$	98.8	0.2	0.0	1.0	0.0	0.0	0.0
		$\bar{N}_{pat}$	16.7	3.5	5.3	8.2	5.3	1.0	
	6	$P_{\%}$	0.2	0.0	0.1	0.0	11.5	88.2	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.0	2.4	6.9	24.7	
	7	$P_{\%}$	0.2	0.0	0.1	17.6	81.0	1.1	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.2	6.4	18.1	9.2	
$U \sim \Gamma(2, 2)$ for linear model									
$U \sim N(0, 1)$ for probit model	1	$P_{\%}$	0.1	0.0	0.0	1.4	97.0	1.5	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.2	5.8	40.4	7.6	
	2	$P_{\%}$	0.4	11.7	73.7	14.0	0.2	0.0	0.0
		$\bar{N}_{pat}$	2.3	7.2	30.0	9.6	5.8	5.1	
	3	$P_{\%}$	99.1	0.3	0.1	0.0	0.0	0.0	0.5
		$\bar{N}_{pat}$	51.7	6.3	1.9	0.1	0.0	0.0	
	4	$P_{\%}$	0.0	0.0	4.2	87.4	8.4	0.0	0.0
		$\bar{N}_{pat}$	2.1	2.1	5.6	34.7	10.3	5.2	
	5	$P_{\%}$	99.0	0.0	0.0	1.0	0.0	0.0	0.0
		$\bar{N}_{pat}$	29.5	3.5	6.4	11.6	7.7	1.3	
	6	$P_{\%}$	0.2	0.0	0.0	0.0	4.5	95.3	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.0	2.4	8.1	43.5	
	7	$P_{\%}$	0.2	0.0	0.0	12.2	86.6	1.0	0.0
Prepared using sagej.cls		$\bar{N}_{pat}$	2.1	2.0	2.2	8.3	34.2	11.2	

Table 6. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). For the activity data was generated from the linear mixed effects model assuming both a random intercept and a random slope for time. Toxicity model was not modified. The optimal dose is in bold and the MTD in italic.

Scenario	Conditions		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
		$(Y_{(l),min}, p_l)$	(71, 0.00)	(64, 0.00)	**(57, 0.03)**	(49, 0.12)	*(39, 0.38)*	(29, 0.75)	
6.1	$\sigma_1 = 1, \sigma_2 = 3$	$P_{\%}$	0.2	10.8	80.3	8.0	0.7	0.0	0.0
	$\sigma_3 = 1$ and $\rho_{\sigma_1,\sigma_3} = 0.7$	$\bar{N}_{pat}$	2.2	7.4	31.1	8.4	5.8	5.0	
6.2	$\sigma_1 = 1, \sigma_2 = 3$	$P_{\%}$	1.0	11.8	67.9	18.2	1.2	0.0	0.0
	$\sigma_3 = 3$ and $\rho_{\sigma_1,\sigma_3} = 0.7$	$\bar{N}_{pat}$	2.6	7.9	26.5	11.6	6.2	5.2	

Table 7. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). For the activity data was generated from a linear mixed effects model that included both a linear and a quadratic term for time. Toxicity model was not modified. The optimal dose is in bold and the MTD in italic.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
7.1	$(Y_{(l),min}, p_l)$	(261, 0.00)	(223, 0.00)	(183, 0.03)	(138, 0.12)	***(89, 0.38)***	(37, 0.75)	
	$P_{\%}$	0.2	0.0	0.0	1.1	97.5	1.2	0.0
	$\bar{N}_{pat}$	2.1	2.0	2.2	5.2	40.6	7.9	

Table 8. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). For the activity data was generated from a linear mixed effects model, with response being associated with increase and progression with decrease of the biomarker, as shown in figure 1. The optimal dose is in bold and the MTD in italic.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
8.1	$(Y_{(l),min}, p_l)$	**(39, 0.02)**	(43, 0.07)	(46, 0.20)	*(49, 0.43)*	(52, 0.68)	(75, 0.88)	
	$P_{\%}$	99.8	0.0	0.0	0.2	0.0	0.0	0.0
	$\bar{N}_{pat}$	32.9	3.6	6.2	10.5	6.0	0.8	
8.2	$(Y_{(l),min}, p_l)$	(44, 0.00)	(53, 0.00)	**(62, 0.03)**	(72, 0.12)	*(81, 0.38)*	(90, 0.75)	
	$P_{\%}$	0.2	6.7	73.7	19.0	0.4	0.0	0.0
	$\bar{N}_{pat}$	2.1	5.1	28.9	12.8	6.6	4.5	

Table 9. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). For scenarios $9.1 - 9.3$ data was generated from a saturated linear mixed effects model for activity and the probit model for toxicity. For scenarios $9.4 - 9.6$ data was generated from the linear mixed effects model for activity and a logistic model for toxicity. The optimal dose is in bold and the MTD in italic.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
9.1	$(Y_{(l),min}, p_l)$	(86, 0.00)	**(73, 0.00)**	(69, 0.01)	(66, 0.04)	(64, 0.13)	*(58, 0.35)*	
	$P_{\%}$	4.1	91.1	4.3	0.5	0.0	0.0	0.0
	$\bar{N}_{pat}$	3.9	30.0	7.6	3.3	3.9	11.3	
9.2	$(Y_{(l),min}, p_l)$	(89, 0.02)	(88, 0.07)	**(66, 0.20)**	*(59, 0.43)*	(48, 0.68)	(33, 0.88)	
	$P_{\%}$	17.6	2.9	76.9	2.5	0.1	0.0	0.0
	$\bar{N}_{pat}$	7.4	3.7	27.2	12.5	7.8	1.4	
9.3	$(Y_{(l),min}, p_l)$	(97, 0.00)	(94, 0.00)	**(81, 0.01)**	(76, 0.04)	(74, 0.13)	*(69, 0.35)*	
	$P_{\%}$	0.2	8.5	59.0	32.0	0.2	0.1	0.0
	$\bar{N}_{pat}$	2.1	5.8	19.5	17.1	3.9	11.6	
9.4	$(Y_{(l),min}, p_l)$	(200, 0.04)	(176, 0.08)	(147, 0.13)	(115, 0.23)	***(79, 0.36)***	(40, 0.54)	
	$P_{\%}$	0.4	0.0	0.2	10.8	66.4	22.2	0.0
	$\bar{N}_{pat}$	2.3	2.4	3.6	9.8	27.4	14.5	
9.5	$(Y_{(l),min}, p_l)$	**(78, 0.10)**	(71, 0.19)	*(62, 0.33)*	(53, 0.51)	(42, 0.72)	(30, 0.88)	
	$P_{\%}$	81.6	17.6	0.4	0.2	0.2	0.0	0.0
	$\bar{N}_{pat}$	30.8	14.8	6.0	5.2	2.6	0.6	
9.6	$(Y_{(l),min}, p_l)$	(193, 0.25)	***(167, 0.40)***	(135, 0.59)	(99, 0.77)	(60, 0.91)	(16, 0.97)	
	$P_{\%}$	13.5	71.5	14.9	0.1	0.0	0.0	0.0
	$\bar{N}_{pat}$	12.4	32.9	12.2	2.1	0.4	0.0	

Table 10. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$), under scenarios 1 and 4 of table 2 of the article. One or more doses were "equally" active to the MTD if their minimum predicted biomarker values did not differ by more than 45 and 10 units/ml for scenarios 10.1 and 10.2, respectively. The optimal dose is in bold and the MTD in italic.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
10.1	$(Y_{(l),min}, p_l)$	(200, 0.00)	(176, 0.00)	(147, 0.02)	**(115, 0.12)**	*(79, 0.38)*	(40, 0.75)	
	$P_{\%}$	0.0	0.0	5.2	90.1	4.7	0.0	0.0
	$\bar{N}_{pat}$	2.0	2.1	6.5	34.4	9.5	5.5	
10.2	$(Y_{(l),min}, p_l)$	(87, 0.00)	(78, 0.00)	(67, 0.03)	(55, 0.12)	***(41, 0.38)***	(26, 0.75)	
	$P_{\%}$	0.0	0.0	0.0	1.8	96.6	1.6	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.3	6.2	39.9	7.6	

Table 11. Sensitivity analysis of 2000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$), under scenario 4 of table 2 of the article. Criteria for joint modeling implementation, minimum number of patients η and maximum accepted parameter estimation standard error (SE) were modified. The optimal dose is in bold and the MTD in italic.

η (SE)	Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
			(87, 0.00)	(78, 0.00)	(67, 0.03)	**(55, 0.12)**	*(41, 0.38)*	(26, 0.75)	
20 (20)	11.1	$P_{\%}$	0.1	0.0	6.4	89.5	4.0	0.0	0.0
		$\bar{N}_{pat}$	2.1	2.0	6.4	34.7	9.5	5.3	
16 (10)	11.2	$P_{\%}$	0.0	0.1	4.7	90.2	5.0	0.0	0.0
		$\bar{N}_{pat}$	2.1	2.2	6.4	35.6	8.6	5.1	
25 (5)	11.3	$P_{\%}$	0.0	0.1	5.7	90.3	3.9	0.0	0.0
		$\bar{N}_{pat}$	2.0	2.0	5.0	32.8	12.2	6.0	